Investigation of neurobiological-genetic correlates and source-informants of attention deficit hyperactivity disorder (ADHD) in adolescents and adults

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Investigation of neurobiological-genetic correlates and source-informants of attention deficit hyperactivity disorder (ADHD) in adolescents and adults

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder associated with wide-spread impairments in behavioural, neurocognitive and biological functions. This thesis aimed to investigate neurobiological and genetic correlates, as well as informant source validity, of ADHD in adolescents and adults using a multi-disciplinary approach. In the first part of the thesis, the aim was to evaluate the validity of informant sources for ADHD by examining associations with cognitive-neurophysiological correlates and future adverse life outcomes using both clinical and epidemiological samples. The findings suggest that both parent- and self-report of ADHD in adolescence and young adulthood may provide some valuable insight into symptoms and impairments, but parent-reports may have higher construct and predictive validity in this age range. In the second part of the thesis, the aims were to further our understanding of different neurobiological and genetic risk factors associated with ADHD, using cognitive-neurophysiological, electrodermal and genetic methods, in both clinical and population samples. Firstly, genetic analyses showed that ADHD risk alleles considered 'en masse', using polygenic risk scores, predicted several frequently co-occurring traits and disorders. These findings suggest that common genetic variation underlying risk for ADHD also contributes to higher body mass index, neuroticism, anxiety and depressive disorders, substance use, risk-taking and lower general cognitive ability in the general population. Secondly, analyses using electrodermal data suggest that abnormal autonomic arousal in ADHD varies as a function of recording context rather than reflecting stable impairments in the disorder. Finally, results from a randomised cross-over trial show that electroencephalogram (EEG) brain measures of executive and sustained attention improved after a single session of high-intensity exercise, suggesting that high-intensity exercise interventions may be appropriate for improving inattentiveness. Overall, this thesis provides insights into the validity of source-informants of ADHD in adolescents and young adults, and the nature of cognitive-neurobiological and genetic correlates of ADHD.

Statement of authorship

This thesis represents my own work, from several collaborative projects. Chapters 2 and 5 include data from a follow-up project of ADHD and control sibling-pairs (Sibling EEG Follow-up Study [SEFOS]; PI: Professor Jonna Kuntsi). The SEFOS project was supported by generous grants from Action Medical Research and the Peter Sowerby Charitable Foundation (grant reference GN1777). The results included in Chapter 3 are based on data from the Swedish Twin Study of Child and Adolescent Development (TCHAD). This was funded by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 667302 (PI: Professor Paul Lichtenstein). The research in Chapter 3 was also supported by a grant (IG2012-5056) from the Swedish Foundation for International Cooperation in Research and Higher Education, which allowed me to undertake a visit to Karolinska Institute, Sweden, to perform the analyses, and a grant from the Swedish Research Council (2014-3931). The results in Chapter 4 included data from the UK Biobank Resource under application number 18177 (PI: Paul O'Reilly) and was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Chapter 4 also used freely available data from the Psychiatric Genomics Consortium (PGC) website (https://www.med.unc.edu/pgc/). Results in Chapter 6 included data from a cross-over study of the effect of physical exercise on cognition and brain function (Physical Activity on Brain Function [PHAB]), supported by my Medical Research Council (MRC) and Institute of Psychiatry, Psychology and Neuroscience (IoPPN) Excellence PhD Studentship.

Data collection for SEFOS was completed by the research team before I started my PhD. For Chapters 2 and 5, where SEFOS data were used, I formulated the research questions, pre-processed skin conductance data, conducted analyses and interpreted the findings under the guidance of Professor Jonna Kuntsi and with additional advice from Dr Celeste Cheung, Dr Sarah Naomi James, Dr Grainne McLoughlin, Professor Daniel Brandeis, Professor Tobias Banaschewski and Professor Philip Asherson. For

Chapter 3, I formulated the research questions, conducted analyses and interpreted the findings under the supervision of Professor Henrik Larsson and Professor Jonna Kuntsi, and with further advice from Andreas Jangmo, Dr Isabell Brikell, Dr Ralf Kuja-Halkola, Dr Amir Sariaslan and Professor Paul Lichtenstein. For Chapter 4, I formulated the research questions, processed data, conducted analyses and interpreted the findings under the guidance of Dr Paul O'Reilly and Professor Jonna Kuntsi, and with additional advice from Kylie Glanville, Dr Jonathan Coleman and Dr Shin Wan Sam Choi. For Chapter 6, I planned the study and collected the data, pre-processed the cognitive and electroencephalogram data, ran analyses and interpreted the findings under the guidance of Professor Jonna Kuntsi and Dr Alan Barker. Isabella Vainieri and Eleonora Infantino helped with data collection, and I received further advice about analyses and interpretation of findings from Dr Giorgia Michelini, Dr Anna Rommel and Professor Philip Asherson.

Publications relevant to this thesis

Chapter 2 is based on the following publication (available under the Creative Commons licence):

Du Rietz, E., Cheung, C. H. M., McLoughlin, G., Brandeis, D., Banaschewski, T., Asherson, P., Kuntsi, J. (2016). Self-report of ADHD shows limited agreement with objective markers of persistence and remittance. *Journal of Psychiatric Research,* 82, 91-99.

Chapter 3 is based on the following publication (available under the Creative Commons licence):

Du Rietz, E., Kuja-Halkola, R., Brikell, I., Jangmo, A., Sariaslan, A., Lichtenstein, P., Kuntsi, J., Larsson, H. (2017). Predictive validity of parent- and self-rated ADHD symptoms in adolescence on adverse life outcomes. *European Child & Adolescent Psychiatry*, 26, 857-867.

Chapter 4 is based on the following publication (available under the Creative Commons licence):

Du Rietz, E., O'Reilly, P., Kuntsi, J. (2018). Association between polygenic risk for ADHD and frequently co-occurring traits and disorders. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging,* 3, 635-643.

Chapter 5 is adapted from the following publication under review:

Du Rietz, E., James, S., Asherson, P., Banaschewski, T., Brandeis, D., Kuntsi, J. (under review). Autonomic arousal in young individuals with ADHD as a function of recording context. *Psychiatry Research.*

Chapter 6 is adapted from the following publication under review:

Du Rietz, E., Barker, A., Michelini, G., Vainieri, I., Rommel, A., Asherson, P., Kuntsi, J. (under review). Beneficial effects of acute high-intensity exercise on electrophysiological indices of attention processes in young adult men. *Behavioural Brain Research.*

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Table of contents

Table of figures

Table of tables

CHAPTER 1 – Introduction

1.1 Abstract

In this introductory chapter, I will give an overview of attention-deficit/hyperactivity disorder (ADHD). I will first summarise diagnostic criteria, categorical and dimensional approaches, epidemiology and informant source validity in ADHD. I will then review the research on the genetic and environmental aetiology of ADHD and discuss neurobiological impairments in affected individuals. Treatments and interventions for ADHD will then be discussed. Finally, I will provide the specific aims of this thesis and discuss how the chapters will address these objectives.

1.2 Introduction to ADHD

ADHD is a neurodevelopmental disorder characterised by developmentally inappropriate levels of inattention, hyperactivity and impulsivity. The concept of ADHD-like problems was first introduced in the medical literature in the late 18th century by the German physician Melchior Adam Weikard in 1775 and the Scottish physician Alexander Crichton in 1798 (Barkley & Peters, 2012). The American Psychiatric Association (APA) first included ADHD, which was referred to as "hyperactive child syndrome", in the Diagnostic and Statistical Manual (DSM) of Mental Disorders in its second edition in 1968 (DSM-II; APA, 1968). This was later updated in the third edition of DSM (DSM-III; APA, 1980), where equal emphasis was placed on the two symptom dimensions, and it was acknowledged that there could be heterogeneity in symptom presentations. This later led to the first distinction between ADHD subtypes (inattentive, hyperactive-impulsive and combined) in DSM-IV and the revised version DSM-IV-TR (APA, 1994; APA, 2000). In the latest DSM version (DSM-5), ADHD is further described into adulthood and the age of onset has been raised from seven years to twelve years, highlighting the possibility of ADHD symptoms emerging in early adolescents. Further, the DSM-5 has lowered the number of symptoms required to meet diagnosis in adults, from six to five symptoms, of either inattention or hyperactivity-impulsivity, and the ADHD subtypes are now termed "presentations",

acknowledging that research shows that subtypes may not be stable across development (Willcutt, 2012).

DSM diagnostic criteria are similar to those included in the International Classification of Disease (ICD-10), which is another diagnostic system by the World Health Organization (WHO) (World Health Organization, 1992). The latest version, ICD-10, refers to ADHD as "hyperkinetic disorder", defined by the presence of symptoms from all three dimensions of inattention, hyperactivity and impulsivity in at least two settings (e.g. at home and at school). The ICD-10 is therefore considered more stringent as it describes a more severe form of ADHD (Sørensen, Mors, & Thomsen, 2005).

1.2.1 Diagnostic criteria of ADHD

The diagnostic criteria used for the studies of clinical ADHD in this thesis have been based on the DSM-IV-TR, as the newer DSM-5 was not yet available during data collection procedures for SEFOS or the PGC. The DSM-IV-TR lists eighteen symptoms of ADHD (Table 1.1), which includes nine inattentive symptoms and nine hyperactive-impulsive symptoms (six hyperactive, three impulsive). An individual is diagnosed with ADHD if they show a minimum of six symptoms from one of the subscales for at least six months and if symptoms are manifested before the age of seven years. According to the DSM-IV-TR, these symptoms should also be associated with functional impairments in at least two settings. Additionally, ADHD symptoms should not occur exclusively during the course of a pervasive developmental or psychotic disorder and should not be better explained by another psychiatric condition. Individuals can be diagnosed with one of three ADHD subtypes: predominantly inattentive-type (ADHD-IA) if they display at least six inattentive symptoms, predominantly hyperactive-impulsive type (ADHD-HI) if they display at least six hyperactive-impulsive symptoms, or ADHD combined-type (ADHD-C) if they display at least six symptoms in both subscales. Adults are diagnosed with ADHD according to the DSM-IV-TR if they first met diagnostic criteria in childhood and symptoms were present before the age of seven years, and if they meet diagnostic criteria in adulthood.

Table 1.1 DSM-IV-TR diagnostic items for ADHD

Inattention
1. Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activity
2. Often has difficulty sustaining attention in tasks or play activities
3. Often does not seem to listen when spoken to directly
4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to comprehension)
5. Often has difficulty organizing tasks and activities
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
7. Often loses things necessary for tasks or activities at school or at home (e.g. toys, pencils, books, assignments)
8. Is often easily distracted by extraneous stimuli
9. Is often forgetful in daily activities
Hyperactivity
10. Often fidgets with hands or feet or squirms in seat
11. Often leaves seat in classroom or in other situations in which remaining seated is expected
12. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
13. Often has difficulty playing or engaging in leisure activities quietly
14. Often talk excessively
15. Is often 'on the go' or often acts as if 'driven by a motor'
Impulsivity
16. Often has difficulty awaiting turn in games or group situations
17. Often blurts out answers to questions before they have been completed
18. Often interrupts or intrudes on others, e.g. butts into other children's games

Note: Diagnostic items replicated from the revised version of the DSM-IV (DSM-IV-TR; APA, 2000)

1.2.2 Categorical and dimensional approaches

The DSM and ICD frameworks use a categorical classification system to diagnose mental disorders such as ADHD. A disorder is classified as present or not present using binary definitions of disorders based on symptoms and impairment. This categorical classification is reflected by binary treatment protocols in clinical practice and has advantages, such as allowing clear diagnostic decisions and effective communication between professionals in health care and research (Coghill & Sonuga-Barke, 2012). This binary classification approach, however, does not reflect the mounting research that suggests that inattentive and hyperactive-impulsive symptoms represent the high end of traits that occur continuously throughout the population (Asherson, Buitelaar, Faraone, & Rohde, 2016). For example, sophisticated statistical modelling approaches, including factor mixture and taxometric procedures, have shown that ADHD represents a continuum of severity (Hudziak et al., 1998; Lubke, Hudziak, Derks, van Bijsterveldt, & Boomsma, 2009). Aetiological research has further shown that genetic influences underlying ADHD (Chen et al., 2008; Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Stergiakouli et al., 2016), and neurobiological correlates (Kuntsi et al., 2010, 2014), are similar across clinically diagnosed ADHD and ADHD symptoms in the population. This research has led to a paradigm shift initiated by the Research Domain Criteria (RDoC) by the National Institute of Mental Health (NIMH) to employ a more dimensional approach for the classification of mental illness (Insel et al., 2010). The RDoC may, however, have limited clinical utility for diagnostic and treatment practice (Brown & Barlow, 2005), as the dimensional approach has a less clear distinction between affected and unaffected individuals and fails to incorporate functional impairment experienced by individuals. Both categorical and dimensional frameworks may be valuable in research in different ways, and both approaches are employed in this thesis to investigate ADHD and its neurobiological correlates.

1.2.3 Epidemiology

1.2.3.1 Prevalence and developmental trajectories

Meta-analyses suggest that the prevalence of ADHD is 5-7% in childhood and adolescence (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012) and around 2-5% in adults worldwide (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009; Willcutt, 2012). While ADHD was initially regarded as a childhood-limited disorder (Hill & Schoener, 1996), research shows that the disorder can persist into adulthood. Adult ADHD has received increasing clinical and research awareness and recognition (Asherson et al., 2016; APA, 2013). The lower prevalence of ADHD in adulthood may be explained by remission of symptoms in ADHD from childhood to adulthood. Another explanation may also be the low recognition of ADHD in adulthood, which in turn can lead to under-diagnosis in later ages. Until the recent DSM-5, the symptoms of ADHD included in the diagnostic manual were based on behavioural descriptions in children (APA, 2000; APA, 2013). Symptoms of hyperactivity-impulsivity in adulthood are often manifested as feelings of restlessness and inner tension (Kooij et al., 2010). If these are not captured by the DSM, the prevalence rate would be lower in adults as a result of under-diagnosis. Further, as clinicians may be less experienced with adult ADHD, it may be likely that adults with the disorder are easily misdiagnosed with another, perhaps more common, adult psychiatric disorder (Asherson et al. 2014).

Numerous studies have found that ADHD symptoms, especially hyperactivity-impulsivity, tend to decline with age (Faraone, Biederman, & Mick, 2006; Pingault et al., 2015; Willcutt, 2012). This has been reflected as remission of ADHD in adulthood, and follow-up studies have attempted to establish the proportion of individuals with childhood ADHD who will remit in adulthood. A meta-analysis of longitudinal studies found that, while ADHD in 15% of individuals diagnosed with the disorder in childhood persisted into young adulthood, 50% of individuals with childhood ADHD met criteria for partial remission, i.e. continued to have impairing symptoms despite failing to meet all DSM-IV diagnostic criteria (Faraone et al., 2006). However, there are large discrepancies in ADHD persistence rates that are derived from different studies.

Recent studies that followed up individuals with clinical childhood diagnosis of the severe ADHD-C type have reported persistence rates into adolescence and young adulthood of 79-87% (Cheung et al., 2015; van Lieshout et al., 2016). Persistence rates from recent birth-cohort studies, however, have been estimated around 1.5-10% (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015; Riglin et al., 2016). One reason for the large discrepancy between population-based and clinical studies in ADHD persistence rates may be that the clinically-referred children with ADHD identified in the clinical studies may have a more severe form of ADHD, compared to non-clinically referred children who did not seek treatment for the ADHD symptoms and impairment. The more severe form of ADHD may be less likely to remit in adulthood, which would lead to higher persistence rates. There have also been wide differences in the criteria adopted to establish ADHD 'persistance' across studies, such as only using ADHD symptoms rather than full ADHD diagnoses, which has been found to have a large effect on persistence rates (Caye et al., 2016; Sibley, Mitchell, & Becker, 2016). Another possible reason for the discrepancy in persistence rates is the different use of source informants during follow-up, which will be discussed in further detail in section 1.3.

Recent findings from population-based studies have now suggested that it may be possible for adults to present with ADHD without having met criteria for diagnosis in childhood (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015), which is required for an ADHD diagnosis according to the ICD and DSM manuals. These studies propose that ADHD can emerge in adolescence-to-adulthood and that this adult-onset ADHD may represent a distinct diagnostic condition from childhood ADHD. This proposal, which redefines how we diagnose adult ADHD, has recently been the topic of controversial debate. Critics have, for example, suggested that these population-based studies (1) overestimate the prevalence of adult-onset ADHD and (2) fail to take into account that childhood ADHD may have been missed, for example due to familial scaffolding. First of all, while childhood ADHD is diagnosed based on parent- and teacher-reports, adolescent and adult ADHD diagnoses have relied on self-reports in

the studies. The use of self-report may have led to less valid and over-estimated reports of ADHD symptoms, a trend which has been found in other population-based research (Merwood et al., 2013) as opposed to clinical studies where self-reports are often under-estimated compared to parents (Barkley, 2002; Sibley et al., 2012). Further, these studies have relied on screening instruments to assess ADHD and have failed to consider alternative causes of ADHD symptoms and to obtain full psychiatric histories of participants (Caye, Sibley, Swanson, & Rohde, 2017). A recent population-based study found that the majority of late-onset ADHD cases were disregarded because of symptoms or impairment occurring exclusively in the context of heavy substance use or another mental disorder (Sibley et al. 2018). Second, researchers have suggested that children may experience sub-threshold ADHD symptoms, which may not reach a full ADHD diagnosis due to positive external scaffolding or protective factors, such as having a supporting family or high IQ (Faraone & Biederman, 2016). When such children face challenges later in development, possibly without the same external scaffolding, their symptoms may become more impairing and in turn reach diagnostic criteria. Adult-onset ADHD is still poorly understood and much more research, addressing these points of concern, is needed to clarify the nature of the condition.

1.2.3.2 Gender differences

The prevalence of ADHD, documented as rates of diagnoses or ADHD symptom count, has consistently been found to be higher in boys than in girls (Willcutt, 2012). Numerous studies report a higher prevalence in boys in childhood, with estimated gender ratios of 3:1 in population-based studies and 9:1 in clinic-referred studies (Polanczyk et al., 2007; Gaub & Carlson, 1997; Staller and Faraone, 2006). In adults, the prevalence rates have been found to be more similar across gender, with estimated gender ratios of 1:1 to 1.6:1 (Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012; Faraone & Biederman, 2005; Kessler, Berglund, et al., 2005).

There are several proposed theories attempting to explain the substantial lower prevalence of ADHD in girls. One possible reason may be that the diagnostic tools

currently used to diagnose ADHD are not suitable to diagnose girls. As current diagnostic criteria were developed on predominantly male samples, they may not be adequately generalisable to female samples (Nussbaum, 2012). Another possible explanation for the gender difference in prevalence rates is that girls with ADHD are underrepresented in childhood due to a gender-based referral bias. ADHD in girls is less often manifested by hyperactive-impulsive symptoms or associated disruptive behaviours than in boys (Biederman et al., 2002; Thorell & Rydell, 2008; Willcutt, 2012). These externalising symptoms and behaviours are often associated with clinical referral, by parents and teachers, and may therefore explain why more boys receive an ADHD diagnosis in childhood. The more similar ADHD prevalence rates seen in adulthood may be explained by the fact that more adult ADHD cases are often self-referred and thus, would not be subject to a gender-based referral bias due to externalising behaviour (Biederman et al., 2004). Alternatively, it may be that adult women with ADHD are more likely to self-refer to mental health services, which would in turn lead to more equal prevalence rates across genders because of an under-diagnosis in adult men (Arcia & Conners, 1998; Biederman et al., 1994). Another possible reason for lower prevalence rates of ADHD in girls is that the disorder in girls could represent a less severe disorder than in boys. However, evidence for this theory has been mixed, with some studies showing that girls show less severe ADHD symptoms than boys (Arnett, Pennington, Willcutt, Defries, & Olson, 2015; Gaub & Carlsson, 1997), but other studies showing the opposite effect (Elkins, Malone, Keyes, Iacono, & Mcgue, 2011) or no gender difference (Novik et al., 2006).

Yet another possible explanation for the gender difference in ADHD prevalence rates in children but not in adults, is a “protective model” in females (Jacquemont et al., 2014). This model suggests that for girls to meet ADHD diagnostic criteria they require more exposure to ADHD risk factors, such as a higher genetic or familial burden than boys as they would be more resilient to developing the disorder. Evidence for this model comes from studies showing that first-degree relatives (co-twins and siblings) of females with ADHD had significantly more ADHD symptoms than co-twins of males

(Martin et al., 2018; Smalley et al., 2000; Taylor et al., 2016), suggesting that females with ADHD may carry a higher familial risk burden for ADHD, indicated by their co-twins having increased symptoms. Recent molecular genetic findings, however, suggest that females with ADHD do not have increased burden of common genetic variants and that autosomal variants show an almost complete overlap between females and males (Martin et al., 2018). Further, it may be that girls need more time to be exposed to sufficient risk factors to reach the criteria for an ADHD diagnosis and therefore have later-onset ADHD than boys. This is supported by the more equal gender ratio of ADHD prevalence in adults.

The difference in prevalence rates between females and males is still, overall, poorly understood and there is a need for more empirical research to investigate the reasons for the discrepancy. The higher rate of ADHD in boys has led to a greater focus on ADHD in boys than in girls in many large-scale studies (e.g. Chen et al. 2008; Kuntsi et al. 2010; Doyle et al. 2000; Klein et al. 2012), which should be considered when interpreting research findings in the literature.

1.2.3.3 Co-occurring conditions and associated life outcomes

Individuals with ADHD are also at an increased risk of a wide range of mental and physical health conditions. Research has, for example, shown that over half of children with ADHD present with another psychiatric comorbidity (Jensen & Steinhausen, 2015; Kraut et al., 2013; Larson, Russ, Kahn, & Halfon, 2011), most commonly conduct disorder (CD) and oppositional defiant disorder (ODD) (Biederman, Newcorn, & Sprich, 1991; Kraut et al., 2013; Larson et al., 2011). Children and adolescents with ADHD also often exhibit academic problems, which may in part be due to the high co-occurrence of specific learning difficulties such as dyslexia, dyscalculia and dysgraphia. A review reported that reading and numerical disorders occurred in 24-38%, and writing disorders in 59-65% of children diagnosed with ADHD (DuPaul, Gormley, & Laracy, 2013). ADHD in children and adults is also associated with impairments in social communication and functioning, which are key component of autism spectrum disorder (ASD) (Polderman, Hoekstra, Posthuma, & Larsson, 2014; Rommelse, Geurts,

Franke, Buitelaar, & Hartman, 2011). Studies have suggested that around 20-50% of individuals with ADHD also display ASD symptoms (Banaschewski, Poustka, & Holtmann, 2011; Polderman et al., 2014; Rommelse et al., 2011).

Numerous clinical and population-based studies also show that ADHD in adults is associated with an increased prevalence for a range of other co-occurring psychiatric conditions compared to the general population. These co-occurring conditions include anxiety (any anxiety disorder: 47% vs 20%), depression (19-33% vs 6-8%), bipolar disorder (BD; 5-19% vs 0.2-3%) (Faraone et al., 2006; Kessler et al., 2006; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Larsson et al., 2013a), schizophrenia (0.8% vs 0.1-0.3%) (Larsson et al., 2013b; McGrath, Saha, Chant, & Welham, 2008), and abuse of alcohol (6-42% vs 3-32%), drugs (2-30% vs 1-12%) and nicotine (42-55% vs 28-31%) (Faraone et al., 2006; Frei, Hornung, & Eich, 2010; Kessler et al., 2006; Kessler, Chiu, et al., 2005; Pomerleau, Downey, Stelson, & Pomerleau, 1995). Several lines of research have investigated the extent to which the same aetiological mechanisms may explain the co-occurrences of these psychiatric conditions with ADHD. Twin studies suggest moderately large shared genetic effects (genetic correlation (r_A)=0.50-0.77) for the co-occurrence of ADHD with depression and anxiety (Cole, Ball, Martin, Scourfield, & Mcguffin, 2009; Michelini, Eley, Gregory, & McAdams, 2015; Schmitz & Mrazek, 2001) and alcohol dependence (Capusan, Bendtsen, Marteinsdottir, Kuja-Halkola, & Larsson, 2015), and family studies suggest that relatives of ADHD probands are more likely to have BD (odds ratio [OR]=1.84-2.54) and schizophrenia (OR=1.71-2.22) (Cole et al., 2009; Faraone, Biederman, & Wozniak, 2012; Larsson et al., 2013b; McGrath et al., 2008; Michelini et al., 2015; Schmitz & Mrazek, 2001), compared to relatives of controls. Emerging, yet limited, molecular genetic studies using genome-wide data have revealed moderate genetic correlations of ADHD with depression (r_g=0.32-0.48), BD (r_g=0.25), schizophrenia (r_g=0.22) and smoking (r_g=0.38-0.48) (Anttila et al., 2016; Demontis et al., 2018; Lee et al., 2013).

Research has further shown that ADHD diagnoses or elevated ADHD symptoms are associated with somatic health conditions, such as higher BMI in children (OR=1.20-1.22) and in adults (OR=1.30-1.55) (Cortese et al., 2016; Nigg et al., 2016), regardless of medication use. Limited but growing research also suggests that the prevalence of asthma (5-24% vs 3-11%) (Fasmer, Halmøy, Eagan, Oedegaard, & Haavik, 2011; Secnik, Swensen, & Lage, 2005), sleep problems or disorders (43-80% vs 12-29%) (Brevik et al., 2017; Fisher et al., 2014; Fuller-Thomson, Lewis, & Agbeyaka, 2016) and migraine (28% vs 19%) are higher in individuals with adult ADHD compared to controls (Fasmer, Halmøy, Oedegaard, & Haavik, 2011; Instanes, Klungsøyr, Halmøy, Fasmer, & Haavik, 2018). Few studies have investigated the aetiological relationships between ADHD and co-occurring somatic conditions; however, emerging evidence points to common genetic mechanisms underlying the common co-occurrence of obesity with ADHD. A recent study found that siblings of obese men had increased risk for ADHD (OR=1.42, 95% CI=1.24-1.63), compared to siblings of men with normal BMI (Chen et al., 2017). Furthermore, two recent genome-wide studies report significant genetic correlations (r_g=0.21-0.26) between BMI and ADHD, identified through linkage disequilibrium score regression (LDSR) (Anttila et al., 2016; Demontis et al., 2018).

Further research using neurobiological, genetic and environmental approaches is needed to identify the common mechanisms underlying these psychiatric and somatic co-occurrences with ADHD to better understand why the conditions frequently occur together. This may in turn be useful for preventing the emergence of other impairing disorders in ADHD, and improve treatment for individuals with co-occurring conditions. In Chapter 4, I further investigate the genetic associations between ADHD and co-occurring traits and disorders using powerful polygenic risk scoring methods.

1.2.4 Summary

ADHD is a common neurodevelopmental disorder that is often first diagnosed in childhood but can persist into adulthood. While childhood ADHD is more prevalent in boys than in girls, approximately half of the adult ADHD population consists of women. The change in the male-to-female ratio of ADHD prevalence from childhood to

adulthood is still poorly understood and more research is needed to reach conclusive explanations. Individuals with ADHD are more likely than the general population to display many co-occurring mental and physical health conditions, and emerging evidence suggests that these co-occurrences are largely due to common genetic mechanisms.

1.3 Informant sources in diagnosing ADHD

Different informant sources for reports of ADHD symptoms and functional impairments may be used to establish an ADHD diagnosis in clinical and research settings, depending on age and availability of informants. In childhood and young adolescence, parent reports, often together with teacher reports, are recommended and commonly used as informant sources (Taylor et al., 2004). Research suggests that teacher and parent reports of ADHD symptoms show low-to-moderate agreement across clinical and population-based samples (r=0.23-0.42) (McLoughlin, Rijsdijk, Asherson, & Kuntsi, 2011a; Mitsis, Mckay, Schulz, Newcorn, & Halperin, 2000; Sollie, Larsson, & Mørch, 2013). The low agreement reflects the fact that each informant may provide slightly different and unique information and points of views on the childrens' behaviour in different settings.

Self-report becomes increasingly important during diagnostic interviews from adolescence into adulthood and is recommended as the primary informant source for adult diagnosis (Kooij et al., 2010). It becomes more difficult in adulthood to collect multi-informant reports and therefore diagnoses are often solely based on self-report in both clinical and research settings (Asherson, 2005). Emerging empirical evidence, however, suggests that young adults with ADHD may underestimate or lack insight into their problems, which raises potential concerns regarding the accuracy of their accounts in research and clinical settings (Faraone & Biederman, 2016; Knouse, Bagwell, Barkley, & Murphy, 2005; Sibley et al., 2012).

1.3.1 Evaluation of informant sources in adolescence and adulthood

Previous research suggests modest agreement between self- and parent-ratings of ADHD symptoms in adolescents and young adults (r=0.16-0.30) (Barkley, 2002; Pierrehumbert, Bader, Thévoz, Kinal, & Halfon, 2006; Wan Salwina, Baharudin, Nik Ruzyanei, Midin, & Rahman, 2013). Adolescents and young adults with ADHD tend to report their ADHD symptoms as less severe than their parents (Barkley, 2002; Guelzow, Loya, & Hinshaw, 2017; Pierrehumbert et al., 2006), which results in lower rates of ADHD persistence into adulthood when based on self-report. This suggests that previous clinical follow-up studies that have relied on self-report may have estimated persistence of ADHD to be lower than studies using parent-report. Follow-up studies of clinical samples in young adulthood have confirmed that lower rates of persistence of ADHD are generally found when based on self-report compared to other informants such as parent-report (Barkley, 2002; Biederman et al., 2009, 2012; Biederman, Petty, Evans, Small, & Faraone, 2010; Klein et al., 2012; van Lieshout et al., 2016).

The exclusive reliance on adult self-report may have contributed to the low ADHD persistence rate of 5% reported by Moffitt et al. (2015), and similar low persistence rates in other recent population-based studies (Agnew-Blais et al., 2016; Caye et al., 2016), which are substantially lower than previous follow-up studies that have relied on both self- and parent-report, reporting persistence rates between 15% and 35% (Biederman et al., 2010; Faraone et al., 2006). The discrepancy could also be explained by differences between population and clinical samples. One exception is a population study by Riglin et al. (2016) that reported a low persistence rate of 3.9% based on parent-report, but this may partly have been due to the short follow-up duration from childhood to 17 years of age and the use of a short 5-item ADHD scale to classify individuals. While adolescents and young adults with diagnosed ADHD tend to report their ADHD symptoms as less severe than their parents (Guelzow et al., 2017; Pierrehumbert et al., 2006), the opposite trend is often found in population-based samples, where self-ratings are higher than parent- or other-ratings (Merwood et al.,

2013; Sibley et al., 2012). This may contribute to inflation in reports of adult-onset prevalence in population samples (Agnew-Blais et al., 2016; Moffitt et al., 2015).

While it is possible that parents over-estimate the persistence of ADHD in their children after their children have left the family environment, the lower persistence rates based on self-report may also reflect under-diagnosis from under-estimated ADHD symptoms and impairments (Faraone & Biederman, 2016; Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014; Knouse et al., 2005). Emerging evidence supports the latter statement, suggesting that self-report of ADHD may be less accurate for capturing symptoms and impairment than parent-report in adolescence and young adulthood. Population-based and clinical studies have found that parent-reported ADHD symptoms show stronger associations with poor school achievement in adolescence and major life events in young adulthood, compared to self-report (Barkley, 2002; Pierrehumbert et al., 2006). Further, twin studies have found that the heritability estimate for ADHD is much lower when based on self-ratings (48%) than parent-ratings or clinically diagnosed ADHD (82-88%) (Larsson, Chang, D'Onofrio, & Lichtenstein, 2014; Merwood et al., 2013), which may partly indicate a rater-bias (Brikell, Kuja-Halkola, & Larsson, 2015). If individuals with ADHD tend to over- or under-estimate symptoms, systematic measurement error is introduced, which would influence the heritability estimates (Brikell et al., 2015). However, there are other possible explanations for the discrepancy in heritability estimates as further explained in section 1.4.1.1.

Further research is needed to establish the validity of different informant sources for ADHD symptoms and impairment across the transitional stage between childhood and adulthood, to inform diagnostic procedures in both clinical and research settings. In Chapters 1 and 2 the construct and predictive validity of self- and parent-reports of ADHD are explored in adolescents and young adults.

1.3.2 Summary

While parent and teacher reports are used to diagnose childhood ADHD in clinical and research settings, self-report becomes increasingly important in adolescence and adulthood. Young individuals with ADHD tend to report their ADHD symptoms as less severe than their parents, which results in lower rates of ADHD persistence into adulthood based on self-report. Emerging evidence is consistent with the possibility that parent-reports in this age group are more reliable; however, more research is needed to understand the validity of informant sources and how they differ.

1.4 Aetiology of ADHD

1.4.1 Genetics

ADHD is a complex disorder with a multifactorial aetiology. Quantitative genetic research during the last decades has established that ADHD runs in families and is largely influenced by genetic factors, while individual-specific environmental factors may also play a limited role. These findings have guided molecular genetic research that have explored the specific variants that underlie the genetic factors contributing to ADHD. There have also been efforts in identifying environmental risk factors in ADHD and studying how they interact with genes. These research efforts have highlighted the complexity of aetiological pathways to ADHD and how much is still to be learned.

1.4.1.1 Quantitative genetic studies

Family studies have consistently reported that relatives (parents and siblings) of children diagnosed with ADHD are more likely to have ADHD than relatives of typically developing children (Faraone et al., 2005). Adoption studies have further found that biological parents and siblings of nonadopted children with ADHD generally have significantly higher rates of ADHD, while adoptive parents of children with ADHD are not significantly different from parents of comparison children without ADHD (Willcutt, 2006). These findings together suggest that ADHD is a heritable disorder that tends to run in families. Numerous twin studies have set out to estimate the heritability of

ADHD. Twin study designs can disentangle environmental and genetic influences underlying traits by comparing identical twins, who share many of the same aspects of their environment as well as their genetic makeup, and non-identical twins, who also share many of the same aspects of their environment but only 50% of their segregating (i.e. varying) genes. Meta-analyses of twin studies on ADHD in children and adolescents converge on heritability estimates of around 70-80% (Nikolas et al., 2010; Faraone et al., 2004). This suggests that around 70-80% of individual variance in ADHD symptoms is due to genetic influences. Most of the remaining variance has been attributed to non-shared environmental influences that are specific to each twin, rather than shared environmental influences that are shared between twins, such as family environments. These twin findings have replicated across gender and ADHD symptom dimensions (Greven, Rijsdijk, & Plomin, 2011; Nikolas & Burt, 2010). Twin study findings have further indicated that ADHD represents the quantitative extreme of symptoms that are continuously distributed throughout the population. This is supported by findings of similar genetic and environmental factors that contribute to ADHD in children across different levels of impairment (Larsson et al., 2012).

While family studies of ADHD in adults have suggested a high degree of familial clustering (Faraone, 2004), most twin studies on adult ADHD have reported much lower heritability estimates (h^2=37-44%) than in childhood and adolescent ADHD (Boomsma et al., 2010; Larsson et al., 2013; Polderman et al., 2013; Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Van Den Berg, Willemsen, De Geus, & Boomsma, 2006). Several lines of research suggest that the lower heritability estimates in older adults with ADHD might not reflect less of a genetic influence underlying ADHD in older ages, but may reflect the use of self-report for ADHD, rather than parent- and teacher-report. The use of self-reports may generate lower heritability estimates if self-assessed ADHD provides a less reliable measure of behaviour (Brikell et al., 2015; Knouse et al., 2005). Low reliability of measures increases measurement error (Franke et al., 2012), which would increase the non-shared environmental component in classical twin modelling and in turn impose a ceiling on heritability

estimates (Brikell et al., 2015; Merwood et al., 2013). This account would, however, not be enough to explain why heritability estimates of ADHD calculated from a different teacher or parent rater for each twin pair, rather than the same rater, have been similarly low as self-ratings (Kan, Van Beijsterveldt, Bartels, & Boomsma, 2014; Merwood et al., 2013). Thus, another plausible explanation for the lower heritability estimates for self-report in adult ADHD is the switch from relying on one informant (e.g. teacher/parent) in childhood for both twins in a pair, to relying on different informants for each twin in adulthood, as twins rate themselves. Agreement between two raters will always be lower than agreement between one rater, thus, twin studies relying on different raters for each twin in a pair may underestimate the twin correlation and heritability (Brikell et al., 2015). Conversely, when the same informant is used to rate both twins in a pair, this may produce inflation in twin correlations and heritability estimates (Freitag, Rohde, Lempp, & Romanos, 2010).

1.4.1.2 Molecular genetic studies

Genome-wide association analyses (GWAS), testing associations of several hundreds of thousands of genotyped common variants (single-nucleotide polymorphisms; SNPs) with an outcome, have previously struggled to identify genetic variants that show reliable and significant association with ADHD, and that explain more than a small fraction of its heritability (Neale et al., 2010; Williams et al., 2012). The difficulty in identifying genetic variants has likely been due to insufficient power and the polygenic nature of ADHD, in that risk is a consequence of a large number of genetic variants, each with very small effects.

The most recent mega-GWAS of ADHD, however, including more than 20,000 ADHD cases and 35,000 controls has for the first time identified 12 independent loci in the genome that are significantly associated with ADHD (Demontis et al., 2018). The statistical power of GWAS allows the investigation of different aspects of the genetic aetiology of ADHD through the creation of polygenic risk scores (PRSs), which are composite scores, created for individuals based on the sum of their risk alleles across the genome, weighted by GWAS-derived effect sizes (more detail in Chapter 4). PRSs

derived from the new mega-GWAS could explain up to 5.5% of variance in ADHD case-control status, when using five different sets of target and independent training samples (Demontis et al., 2018). These genetic association studies, together with twin study findings (Larsson et al., 2012), suggest that ADHD is largely explained by common genetic variants that are continuously distributed throughout the population.

The SNP-based heritability based on the mega-GWAS sample (Demontis et al., 2018), i.e. the estimated amount of variance due to genotyped variants that commonly occur throughout the population, was estimated at 0.22, which is still noticeably lower than estimates from twin studies that incorporate both common and rare genetic variants. Thus, a proportion of heritability is likely to be explained by more penetrant, rare genetic variants (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2015; Williams et al., 2010). A genome-wide analysis of rare copy number variants (CNV), with less than 1% population frequency, found enrichment of large, rare CNVs in children with ADHD compared to controls and identified duplications at a specific locus with a relatively large effects size of OR=2.22 (Williams et al., 2012). The successes in recent genetic studies on ADHD as a result of the growing sample sizes and technological advances have provided important insights into the aetiological underpinnings of ADHD and comorbid conditions and will allow for more advanced future genetic investigations.

1.4.2 Environmental risk factors and gene-environment interplay

Genetic studies have demonstrated that genes do not fully account for the risk of developing ADHD and several environmental risk factors have been suggested as being associated with the disorder. These putative environmental risk factors include pre-natal smoking and alcohol-use, prematurity and low birth weight, diet and family adversity (Sciberras, Mulraney, Silva, & Coghill, 2017; Thapar, Cooper, Eyre, & Langley, 2013). While several studies have reported significant associations between these environmental factors and ADHD, findings have not always replicated and studies have often failed to account for familial confounding, e.g. genetic risks that confer risk to both the risk factor and ADHD and other unmeasured familial factors shared between individuals in the same family (Sciberras et al., 2017; Thapar et al., 2013). One

approach that studies have taken to account for the unmeasured confounding has been sibling-comparison designs. In sibling-comparison studies, siblings are compared to estimate effects of individual-specific environmental effects while controlling for genetic and environmental effects that make siblings within a family similar. Research has shown that while controlling for unmeasured confounding using sibling-comparison designs, or other similar genetically sensitive designs such as the in vitro fertilisation (IVF) design, the associations between ADHD and prenatal smoking and anti-depressant use, maternal BMI and family adversity were no longer significant, which questions the causality of these risk factors on ADHD (Chen et al., 2014; Laugesen, Olsen, Andersen, Frøslev, & Sørensen, 2013; Sciberras et al., 2017; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014; Thapar et al., 2009). Other environmental risk factors, such as prematurity and low birth weight, may be causally associated with ADHD independent of other unmeasured confounding, however more research is needed controlling for other risks, such as smoking or alcohol use during pregnancy and familial confounding to establish the causality of these associations (Sciberras et al., 2017).

It has been increasingly recognised that the relationship between genetic and environmental influences underlying ADHD is likely complex, as these factors may interact in different ways (Thapar, Harold, Rice, Langley, & O'Donovan, 2007). Genetic and environmental factors may interact (gene-environment interaction), such that certain environmental risk factors may contribute to ADHD only in individuals who have a particular genetic predisposition. An individual's genetic predisposition may also increase the likelihood for them to be exposed to a certain environmental risk factor (gene-environment correlation), which might lead for example to inflated heritability estimates in twin studies. The complex interplay between genes and environments leads to difficulties when trying to identify genetic or environmental risk factors separately, and only a relatively small number of studies have studied the interplay between them in ADHD. Research has, for example, suggested that certain variations of genes involved in dopaminergic and serotonergic neurotransmission (e.g.

DAT1, COMT, 5-HTTLPR) moderate the adverse risk of early institutional deprivation, lower birth weight, perinatal substance use and stress on ADHD (Brookes et al., 2006; Kahn, Khoury, Nichols, & Lanphear, 2003; Stevens et al., 2009; Van Der Meer et al., 2014). However, replications of these findings are needed to determine the role of gene-environment interplay in ADHD, and so far, some of these findings have proven difficult to replicate (Gould, Coventry, Olson, & Byrne, 2018; Nigg, Nikolas, & Burt, 2010).

1.4.3 Summary

In this section I first reviewed how quantitative genetic research has established that ADHD is largely influenced by genetic factors, but also by individual-specific environmental factors. These findings have guided molecular genetic research, and recently a mega-GWAS successfully identified 12 loci in the genome that were significantly associated with ADHD. There have also been efforts in identifying environmental risk factors in ADHD, which has been proven difficult due to the complex relationship between genetic and environmental factors. More research is needed to establish the specific genetic and environmental risk factors underlying ADHD, and the complex interactions and correlations by which they operate.

1.5 Neurobiological impairments in ADHD

Cognitive, neurophysiological and electrodermal studies in ADHD aim to identify neurobiological correlates of ADHD to elucidate the mechanisms underlying impairing symptoms. A greater understanding of impairments related to ADHD on a neurobiological level may provide insights into the mechanisms involved in the pathways that lead to the clinical manifestation of ADHD. Such insights may prove beneficial for clinical diagnostic procedures, as well as inform targets for treatment of symptoms. In this section, I will review the literature on cognitive, neurophysiological and electrodermal impairments in ADHD, with an emphasis on deficits relevant to this thesis.

1.5.1 Studies of cognitive impairments

Executive function (EF) is an umbrella term for several higher cognitive functions including response inhibition, planning and working memory. EFs have consistently been found to be impaired in individuals with ADHD, and a meta-analysis of 83 studies report medium effect sizes (Cohen's d=0.46-0.69) for EF impairments in children and adolescents with ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Particularly large effect sizes were found for response inhibition, vigilance, working memory and planning (Willcutt et al., 2005). Studies have revealed similar impairments in adults with ADHD (Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Mowinckel, Pedersen, Eilertsen, & Biele, 2015).

Individuals with ADHD also tend to show difficulties with focusing their attention over an extended period of time, which can be assessed using continuous performance tasks (CPTs). CPTs require participants to detect target stimuli among a sequence of distractor stimuli and respond to them by for example pressing a button (described in more detail in Chapters 2, 5 and 6). The CPT is designed to measure omission errors (OE), which are errors where participants fail to respond when they are expected to and reflect sustained attention. Other performance measures can also be obtained such as commission errors (CE), when participants respond to non-target stimuli and reflect poor response inhibition, and reaction time measures, including reaction time variability (RTV), which reflects intra-individual fluctuations in reaction times. A meta-analysis of 47 studies found that children with ADHD consistently showed increased OE, CE and RTV (d=0.55-0.62) during CPTs compared to controls (Huang-Pollock, Karalunas, Tam, & Moore, 2012).

A similar cognitive task, the Go/NoGo task, including Go and NoGo stimuli, is well-designed to measure CEs as it has a higher target-to-non-target ratios than a CPT (more target stimuli and fewer distractor stimuli). A meta-analysis of 30 studies using Go/NoGo tasks found that children with ADHD showed increased CEs during task performance with moderate-to-large effects and the standard mean difference ranged

from 0.37 to 0.57 (Metin, Roeyers, Wiersema, Van Der Meere, & Sonuga-Barke, 2012). Similar results of impaired sustained attention (Antshel et al., 2010; Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007) and response inhibition (Bekker et al., 2005; Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2010; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005) have been found in adults. The Eriksen flanker task is another performance task often used to study cognitive and neurophysiological impairments in ADHD, where target stimuli are presented with congruent or incongruent flanking stimuli (described in more detail in Chapter 6). The Eriksen flanker task is designed to measure cognitive processes of performance monitoring, inhibitory control and interference control, which have successfully distinguished between ADHD and control groups in both children and adults (Albrecht et al., 2008; McLoughlin et al., 2009; Michelini et al., 2016a).

ADHD is also associated with slower and more variable reaction times relative to controls on cognitive tasks requiring a speeded response. A meta-analysis of 319 studies reported a substantial effect size of RTV in children and adolescents with ADHD (Hedges' g=0.76) and a medium effect size in adults with ADHD (g=0.46) (Kofler et al., 2013) across a range of cognitive tasks, suggesting that high RTV is a consistent feature of ADHD. A meta-analysis of mean reaction times (MRT), obtained during continuous performance tasks, suggests a more modest effect size for increased MRT (d=0.37) (Huang-Pollock et al., 2012). Studies have further found that RTV decreases more among individuals with ADHD than controls during more stimulating task conditions (faster and with reward) (Andreou et al., 2007; Cheung et al., 2017; Kuntsi et al., 2013), suggesting that RTV is not a stable deficit but rather malleable and may be explained by deficits in arousal regulation or attentional allocation (James, Cheung, Rijsdijk, Asherson, & Kuntsi, 2016; Sergeant, 2005). The Fast task is a four-choice reaction time task with two conditions; the slow, unrewarded baseline condition has been found to consistently capture the characteristic slow and variable reaction times in individuals with ADHD, which improve in a fast, rewarded condition (Andreou et al., 2007; Cheung et al., 2016; Tye et al., 2016) (more detail in Chapters 2, 5, and 6).

ADHD has also been associated with lower IQ scores. A meta-analysis of children with ADHD and controls reported an average difference of 7 to 11 points (Frazier et al., 2004) and population-based studies have reported moderate negative correlations between IQ and ADHD symptoms (r=-0.20-0.40) (Kuntsi et al., 2004; Rommel, Rijsdijk, Greven, Asherson, & Kuntsi, 2015; Wood, Asherson, Van Der Meere, & Kuntsi, 2010). Several studies have suggested that higher IQ scores predicts better ADHD outcome among individuals with a diagnosis (Agnew-Blais et al., 2016; Cheung et al., 2015; Gao et al., 2015).

1.5.2 Studies of neurophysiological impairments

Complementing the literature on cognitive-performance deficits in ADHD, research has also outlined abnormalities in brain activity during task performance, reflecting a more direct measurement of covert neurophysiological processes that underlie the cognitive processes (Luck, 2005). A neuroimaging technique which has proven suitable in delineating the neurophysiological impairments in ADHD is electroencephalography (EEG), which allows direct investigation of underlying neural processes with millisecond temporal resolution. EEG measures electrical activity across the scalp, capturing brain voltage fluctuation generated by post-synaptic potential changes from groups of simultaneously active and similarly oriented cortical cells (Buzsáki & Draguhn, 2004).

Research using other neuroimaging methods, particularly functional Magnetic Resonance Imaging (fMRI), have revealed that ADHD is associated with abnormalities across several partially separate neural systems. These include networks involved in executive cognitive functions, such as hypoactivation in the fronto-parietal network, as well as non-executive (e.g. reward) functions, such as hyperactivation in the default mode and the ventral-attentional networks (Castellanos & Proal, 2012; Cortese et al., 2012). A recent cross-sectional mega-analysis of structural MRI brain scans of subcortical and intracranial structures in individuals with ADHD and controls, further reported reduced volumes of several brain regions in ADHD including the

hippocampus, accumbens and amygdala, with the most pronounced effects in childhood (Hoogman et al., 2017). The largest effect sizes were found for the amygdala, which is implicated in emotional regulation problems (Hoogman et al., 2017). Functional and structural MRI techniques are useful for detecting brain regions and patterns of connectivity implicated in cognitive processes, behaviours and disorders, as they produce high-resolution images of the brain and its activity. These techniques do have their limitations however, as they are expensive and bulky to use in testing conditions. Furthermore, fMRI has poor temporal resolution and measures brain activity indirectly through magnetic changes associated with blood oxygen flow in areas of the brain. While EEG only captures brain activity at a scalp level and has poor spatial resolution, it is a direct measure of brain activity, has excellent temporal resolution, and can be portable, allowing for testing outside of laboratory settings.

1.5.2.1 Quantitative EEG

One way to examine EEG data is to measure spontaneous brain activity across a resting-state or task condition. As the EEG data consist of overlapping brain oscillations at different frequencies across power spectra, these can be decomposed from the measured data. Spectral decompositions, such as the Fast Fourier Transform (FFT), can delineate the activity into the different frequency bands. These bands are measured in hertz (Hz), i.e. cycles per seconds and are often divided into delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz) and gamma (>30 Hz) (Loo & Makeig, 2012), although the cut-offs for each band may vary slightly between studies (see Figure 1.1). These frequency bands have demonstrated high test-retest reliability (0.71-0.95), especially the theta and delta bands (>0.85) (Williams et al., 2005). The grouping of these different frequency bands has shown to have functional significance, as each of them has been found to be associated with different aspects of neural processes and behaviour. Traditionally, the frequency bands are examined during resting-state, where delta activity has often been associated with sleep and drowsiness, theta activity with arousal and conflict processes, alpha activity with wakeful relaxation and attentiveness, and beta activity with concentration and motor processes (Hughes & John, 1999; Klimesch, 2012; Uhlhaas & Singer, 2006).

Quantitative EEG (QEEG) is a measure of amount of power within frequency bands and has often been used to characterise atypical neurophysiological profiles in psychiatric disorders.

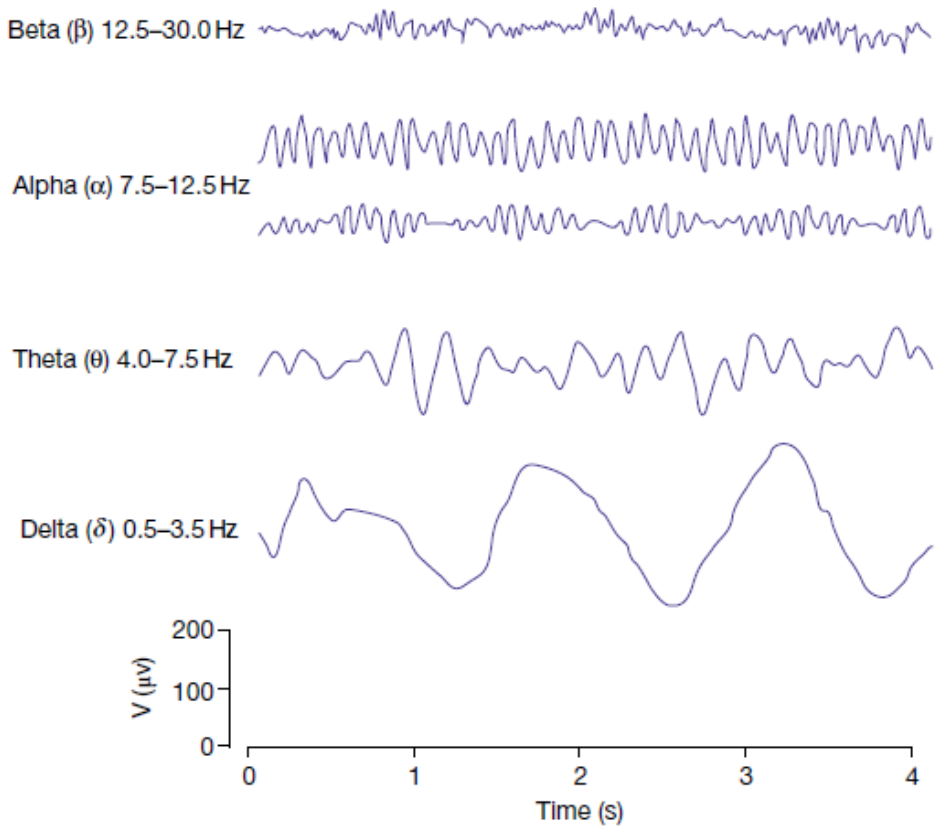

Figure 1.1 EEG frequency bands. Adapted from Tye et al. (2011).

QEEG studies have highlighted several aspects of atypical brain activity in children and adults with ADHD across resting-state and task conditions (Tye et al., 2011; 2012; Kitsune et al., 2015; Loo et al., 2009; 2010; Loo & Makeig, 2012). For example, individuals with ADHD often display increased power in slow (delta and theta) frequency bands and decreased power in fast (beta and alpha) bands during resting-state conditions (Kitsune et al., 2015; Loo et al., 2009; Snyder & Hall, 2006; Tye et al., 2012; Tye, McLoughlin, Kuntsi, & Asherson, 2011). Research has further suggested an imbalance in slow and fast wave brain activity in individuals with ADHD. This is

indicated by increased theta/beta ratio, compared to controls, with meta-analytic evidence suggesting an effect size of 3 and sensitivity and specificity of 94% (Snyder & Hall, 2006). The large effects sizes and high classification accuracy of the theta/beta ratio led the Federal Drug Administration in the USA to approve the ratio as an aid for clinicians during ADHD evaluations, along with standard diagnostic procedures (Snyder, Rugino, Hornig, & Stein, 2015). More recent studies, however, have failed to replicate the increased theta/beta ratio in ADHD populations (Arns et al., 2016; Loo et al., 2013; Rommel et al., 2016; Saad, Kohn, Clarke, Lagopoulos, & Hermens, 2015; Skirrow et al., 2015), which questions the validity of it being regarded as a putative biomarker for ADHD and being used to aid the diagnostic procedure (Arns et al., 2016). QEEG obtained during performance of tasks, such as the CPT, has also been used to study atypical patterns of brain activity in ADHD, but the research is more limited and has produced inconsistent findings. While some studies have reported elevated alpha and theta activity during task performance in individuals with ADHD, relative to controls (El-Sayed, Larsson, Persson, & Rydelius, 2002; Nazari, Wallois, Aarabi, & Berquin, 2011; Swartwood, Swartwood, Lubar, & Timmermann, 2003), other studies have reported no differences between groups (Loo et al., 2009; Rommel et al., 2016; Skirrow et al., 2015). These inconsistencies in findings may, in part, be attributed to differences between age groups of samples or tasks used in the studies.

1.5.2.2 Event-related potentials

Event-related potential (ERP) approaches take advantage of the excellent temporal precision of EEG measurement, as ERPs reflect increases in voltage that are time-locked to an event. Typically, a participant's ERP response to a specific stimulus in a task is averaged across all trials to produce an averaged ERP response, to remove any EEG oscillations unrelated to the stimulus, i.e. "noise". ERP components are used to describe the alternating positive and negative peaks of the ERP waveform (Luck, 2005) and components are quantified by obtaining their amplitude (i.e. magnitude) in microvolt (μV), and latency (i.e. timing in milliseconds) of the brain activity that contributes to each component (Figure 1.2) (Rusnáková & Rektor, 2012). Researchers have often used CPT and Go/NoGo paradigms to elicit ERP components that are

especially implicated in ADHD. A modified version of the CPT, the cue CPT with flankers (CPT-OX), has often been used to study cognitive processes relating to attention, response preparation and inhibitory control in individuals with ADHD (Banaschewski et al., 2003; Van Leeuwen et al., 1998) and is used in Chapters 2, 5 and 6. In the CPT-OX, participants are exposed to Cue stimuli that precede both Go and NoGo stimuli and are asked to respond only when the Go stimuli follow the Cue stimuli. ERPs that are time-locked to the different stimuli reflect different covert processes. For example, the P3 is a late positive component evoked from stimulus presentation, which is thought to reflect (1) executive attention when evoked by the Go stimuli, (2) response inhibition when evoked by the NoGo stimuli and (3) attention orientation when evoked by the Cue stimuli (Banaschewski et al., 2003; Van Leeuwen et al., 1998).

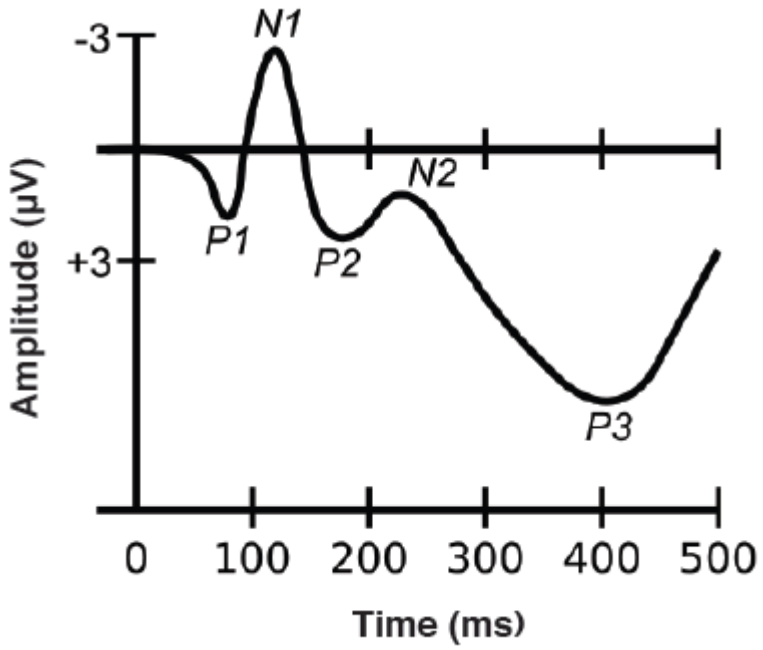

Figure 1.2 Simulated ERP waveform with typical components and naming conventions. Adapted from Rusnakova & Rektor (2012).
Note: Negative voltage is plotted upwards.

Studies of ADHD using the CPT and Go/NoGo paradigms have often demonstrated attenuated ERP components, relating to a range of cognitive processes, across ages (Albrecht et al., 2013; Cheung et al., 2016; Geburek, Rist, Gediga, Stroux, & Pedersen,

2013; Tye et al., 2011). For example, several studies have reported an attenuated fronto-central P3 component in response to NoGo stimuli (NoGo P3) in individuals with ADHD, which is thought to reflect poor response inhibition (Albrecht et al., 2013; Banaschewski et al., 2003; McLoughlin et al., 2010). Studies have also reported an attenuated parietal P3 component (Cue P3) and central contingent negative variation (CNV) following Cue stimuli using the CPT-OX task in individuals with ADHD, which reflect atypical attention orienting and response preparation, respectively (Cheung et al., 2016; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013; McLoughlin et al., 2010). Another, although less consistent, finding is an attenuated P3 to target stimuli in individuals with ADHD, which is thought to reflect atypical attention allocation during response execution (Cheung et al., 2017; Grane et al., 2016; Groom et al., 2010; Szuromi, Czobor, Komlosi, & Bitter, 2011). This finding has, however, not consistently replicated in other studies (Albrecht et al., 2013; Groom et al., 2008; McLoughlin et al., 2010), which may indicate that ADHD case-control differences may depend on the specific cognitive task or paradigm used.

Studies have further found that ADHD is associated with atypical ERP components during performance monitoring paradigms (used in Chapter 6), such as Eriksen flanker tasks, which index goal-directed behaviours to monitor ongoing performance and adjust response selections. These studies have for example found that children and adults with ADHD show reduced frontal N2, which reflects conflict monitoring arising from two competing responses and evaluation of the correct response (McLoughlin et al., 2009; Michelini et al., 2016a; Wild-Wall, Oades, Schmidt-Wessels, Christiansen, & Falkenstein, 2009). Reduced N2 components have generally not been found in studies using the CPT-OX (Doehnert et al., 2013; McLoughlin et al., 2010, 2011), which may indicate that these impairments are only evident in higher-conflict monitoring paradigms (McLoughlin et al., 2009). Studies in children and adults with ADHD have further reported performance monitoring impairments of atypical error-related negativity (ERN) and error-related positivity (Pe), two ERP components that underlie error processing when an incorrect response has been made. A reduced fronto-central

ERN, reflecting impaired automatic error processing, has been found in individuals with ADHD during flanker tasks (Albrecht et al., 2008; Geburek et al., 2013; McLoughlin et al., 2009), however findings have been mixed, especially when using Go/NoGo paradigms (Groom et al., 2013; O'Connell et al., 2009). Similarly mixed findings have been found for the Pe, which is thought to reflect conscious error processing (Bjoern Albrecht et al., 2008; Groom et al., 2013; McLoughlin et al., 2009; Michelini et al., 2016a; O'Connell et al., 2009). Inconsistent ERP findings in the literature on performance monitoring may be due to the variability across studies in how they measure the components, such as peak amplitude or area amplitude, as well as the modest sample sizes of most investigations into these ERPs.

1.5.3 Studies of autonomic arousal

Research further suggests that individuals with ADHD show abnormal profiles in autonomic arousal, which reflects changes in electrodermal activity obtained from electrodes on the skin surface. Electrodermal activity is a sensitive index of sympathetic nervous system (SNS) activity, a system that plays a key role influencing arousal and alertness and is part of the autonomic system (Boucsein, 2012; Dupuy, Clarke, Barry, Selikowitz, & McCarthy, 2014; Van Lang et al., 2007). Investigations of electrodermal activity rely on the assumption that the skin has electrical properties that can be altered in a short time frame, are influenced by the SNS and show associations with cognitive states (Boucsein, 2012). Increased activation of the SNS stimulates sweat gland activity in turn increases skin conductance (SC), an index of electrodermal activity (Figure 1.3). SC is commonly measured through electrodes on the palms or fingers of the non-dominant hand. A very small constant voltage (0.5 Volt) is applied across the electrodes to measure the current flow and in turn determine how well the skin conducts electricity. SC (expressed in microSiemens) can be measured as SC level (SCL), which represents a tonic level of arousal averaged across a time-window, usually resting-state or cognitive performance, or SC responses (SCRs), which represent a phasic change in SC (Boucsein, 2012; Figner & Murphy, 2010). SCRs can be obtained as averaged time-locked components to a specific event, e.g. stimuli in a cognitive task, or be obtained as non-specific SCRs, also called non-

specific fluctuations (NSFs), which can be studied across a whole time-window during resting-state or task performance. Chapter 5 in this thesis will focus on SCL, which indexes increased peripheral arousal, and NSFs, which indexes more variability in peripheral arousal (Boucsein, 2012), in relation to ADHD.

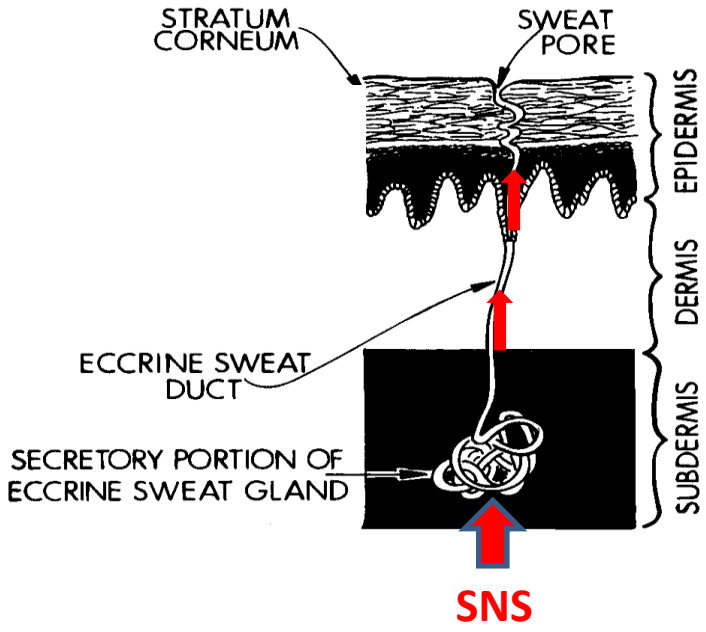

Figure 1.3 An eccrine sweat gland. Adapted from Hassett (1978).

The sympathetic nervous system (SNS) stimulates the production of sweat in the secretory portion of eccrine sweat glands in the subdermis layer of the skin. Sweat rises up to sweat pores in the epidermis layer of the skin, through eccrine sweat ducts in the dermis layer of the skin.

Numerous studies have found that children with ADHD have lower levels of SCL, indicating hypo-arousal during resting-state and task conditions (Barry et al., 2012; Conzelmann et al., 2014; Dupuy et al., 2014; Iaboni, Douglas, & Ditto, 1997; Lazzaro et al., 1999; Mangeot et al., 2001; Mangina, Beuzeron-Mangina, & Grizenko, 2000; O'Connell, Bellgrove, Dockree, & Robertson, 2004). Research is however more limited in adults, where findings have been mixed and inconclusive (Hermens et al., 2004;

Mayer, Wyckoff, & Strehl, 2016). One study found that lower SCL in ADHD was reported in a slow, unrewarded reaction time task, but normalised in a faster, incentive task, suggesting that hypo-arousal can be modifiable in ADHD (James et al., 2016). Mixed findings, mainly from studies on children and adolescents with ADHD, have also emerged for NSFs in the skin conductance. Several studies have reported significantly fewer NSFs in individuals with ADHD compared to controls during resting-state (Beauchaine, Katkin, Strassberg, & Snarr, 2001; Crowell et al., 2006; Satterfield & Dawson, 1971), while other studies report no significant difference (Beauchaine et al., 2015) or an effect in the opposite direction (Pliszka, Hatch, Borcherding, & Rogeness, 1993). Further research is needed using larger sample sizes and where effects are examined across contexts, to clarify these inconsistencies in the SC literature. In Chapter 5 we discuss this further in a study where SC profiles of individuals with ADHD are examined across a long testing assessment in a large sample of adolescents and young adults with ADHD and controls.

1.5.4 Summary

In this section, I have reviewed cognitive tasks that are commonly used to study cognitive-performance and neurophysiological impairments in ADHD. Overall, research has shown that ADHD is associated with a range of neurobiological impairments relating to attentional orienting and lapses, response inhibition and preparation, conflict monitoring and autonomic arousal, amongst others, during resting-state and task performance. I have reviewed studies on brain activity using the EEG approach, as this is the methodology used in the data-based chapters, but other neuroimaging methods are largely in line with the cognitive-electrophysiological abnormalities reported. fMRI studies, for example, indicate that ADHD is associated with abnormalities across several partially separate neural networks involved in executive as well as non-executive cognitive functions, including hypoactivation in the fronto-parietal network and hyperactivation in the default mode and the ventral-attentional networks (Castellanos & Proal, 2012; Cortese et al., 2012).

1.6 Treatment and interventions for ADHD

As ADHD can be a highly impairing disorder and is often associated with adverse outcomes, it is important that affected individuals receive continued support and treatment for their symptoms. In this section the literature on the effectiveness of pharmacological and non-pharmacological treatments for ADHD will be reviewed. I will also describe in more detail the beneficial effects of physical exercise on ADHD and related impairments.

1.6.1 Pharmacological and non-pharmacological treatments

The National Institute of Health and Care Excellence (NICE) guidelines recommend pharmacotherapy for children and young people with ADHD only if their symptoms are still causing impairment in at least one domain after environmental modifications have been implemented (NICE, 2018). Cognitive behavioural therapy (CBT) is recommended for young people with ADHD who have benefited from medication but whose symptoms are still causing impairments. Parent training along with group-based ADHD-focused support is recommended for children and adolescents with severe impairments or comorbid symptoms of oppositional defiant disorder and conduct disorder (ODD/CD). Pharmacotherapy is also recommended for adults with ADHD whose symptoms are still causing significant impairment after environmental modifications have been implemented (NICE, 2018). Non-pharmacological treatment is recommended in combination with medication for adults with ADHD who have benefited from medication but are still experimenting significant impairments in at least one domain. The first-line medication for ADHD is the psychostimulant methylphenidate, although other common medications are dexamphetamine, and non-stimulant drug treatments with atomoxitine (NICE, 2018; Retz, Retz-Junginger, Thome, & Rösler, 2011).

A large body of research, including meta-analytic evidence, suggests beneficial effects of drug treatments on ADHD, with moderate-to-large effect sizes across studies in both children and adults (Chan, Fogler, & Hammerness, 2016; Gayleard & Mychailyszyn, 2017; Maneeton et al., 2015; Prasad et al., 2013). A recent meta-analysis of 185

randomised clinical trials and 243 non-randomised studies questioned the beneficial effects of stimulant medication and its safety for children and adolescents with ADHD (Storebø et al., 2015) because of low quality of clinical trials and associated adverse events such as sleep problems and decreased appetite; however, several major flaws of this study have been highlighted by other scientists in the field (Banaschewski et al., 2016; Mulder, Hazell, Rucklidge, & Malhi, 2016). For example, Storebø and colleagues added their own item on the Cochrane protocol to the quality of measures that was used to deem studies as 'low quality' and the average duration of evaluation of the effects of medication was only 75 days, which may have been too short of a duration to pick up the beneficial effects of medication.

It is also important to thoroughly investigate the effectiveness of non-pharmacological treatments, as some individuals wish to avoid taking medication and as almost one third of individuals with ADHD experience non-effectiveness or intolerable side effects from treatment (Biederman, Spencer, & Wilens, 2004). Behavioural interventions are recommended as non-pharmacological treatment in the NICE guidelines. Meta-analyses of randomised control studies indicate that when outcomes are rated by blinded reviewers, there are significant small-to-medium beneficial effects of behavioural interventions on child and parent functioning, but non-significant effects on core ADHD symptoms (Daley et al., 2014; Sonuga-Barke et al., 2013). The lack of significant effects on core symptoms may be attributed to the potentially poor validity of probably blinded measurements of outcomes; these are often based on small snapshots of behaviour or are rated by teachers who may not know the child well (Sonuga-Barke et al., 2013), or due to variability in effectiveness of different behavioural interventions. Other non-pharmacological interventions that have been developed are psychological, such as cognitive training, mindfulness and neurofeedback (Cortese et al., 2015; van Doren et al., 2018), and dietary treatments, such as restricted elimination diets and free fatty acid supplementation (Nigg & Holton, 2014; Pelsser, Frankena, Toorman, & Pereira, 2017). Yet, blinded evidence for reductions of non-pharmacological treatments on core ADHD symptoms in controlled,

randomised studies are highly needed as limited small effects have only been reported for few-foods diets, artificial food colour exclusion and neurofeedback (Pelsser et al., 2017; Sonuga-Barke et al., 2013; van Doren et al., 2018).

1.6.2 Exercise as a protective factor and potential intervention

Physical exercise has emerged as another putative non-pharmacological intervention for ADHD and initial evidence suggests that it may work as a potential protective factor, increasing adaptive functioning, in individuals with ADHD (Rommel, Lichtenstein, et al., 2015; Rommel, Halperin, Mill, Asherson, & Kuntsi, 2013). Emerging but limited studies using experimental designs have even showed that a single bout of acute exercise can facilitate performance and brain processes during cognitive tasks in individuals with a diagnosis. Studies that have employed acute (short-lived) exercise paradigms of moderate and high intensity and sufficient duration (20 minutes or longer) have reported improvements on cognitive performance measures of EF, attention, vigilance, response accuracy, reaction time and even scholastic achievement (reading and arithmetic tests), in children and young adults with ADHD (Chang, Liu, Yu, & Lee, 2012; Gapin, Labban, Bohall, Wooten, & Chang, 2015; Piepmeier et al., 2015; Pontifex, Saliba, Raine, Picchietti, & Hillman, 2013). Few studies have explored the effects of acute exercise on brain measures underlying cognitive processing in individuals with ADHD, but limited evidence suggest beneficial effects of larger P3 amplitudes during a flanker task, indicating improved attention allocation (Pontifex et al., 2013) and smaller CNV amplitude following a No-Go stimulus, indicating improved response preparation (Chuang, Tsai, Chang, Huang, & Hung, 2015).

A greater number of studies have investigated the acute effects of exercise on cognitive performance and brain measures in the general population. As research suggests that ADHD symptoms and associated neurocognitive impairments may reflect the extreme end of continuous traits and measures distributed throughout the population (Kuntsi et al., 2014; Larsson et al., 2012), studying these measures in healthy populations will also be informative for understanding ADHD. Positive effects, particularly of acute exercise sessions of 20 minutes or more in duration, have been

reported in experimental studies on a range of cognitive performance measures. These measures include inhibition and interference control (effect size; ES=0.25-0.46), attention (ES=0.42), mean reaction time (MRT) (ES=0.30-1.41) and short-term memory (ES=0.26) (Chang, Labban, Gapin, & Etnier, 2012; McMorris & Hale, 2012; McMorris, Sproule, Turner, & Hale, 2011; Roig, Nordbrandt, Geertsen, & Nielsen, 2013; Verburgh, Königs, Scherder, & Oosterlaan, 2014). Several studies suggest that effects are largest for executive functioning, such as response inhibition and interference control (Chang et al., 2012b; Kramer & Erickson, 2007; Tomporowski, Davis, Miller, & Naglieri, 2008), but relatively few studies have investigated effects on measures of attention and attentional lapses. Findings on executive functioning and processing speed have also been mixed, as some studies have failed to replicate the beneficial effect of acute exercise (Coles & Tomporowski, 2008; Wang et al., 2015). These inconsistent findings might be explained by differences in the experimental paradigms used, such as the intensity of exercise, fitness level of participants and time lapse after exercise (Chang et al., 2012a), as well as by differences in the tasks and aspects of cognitive functions being studied.

Further beneficial effects of acute exercise in children and adults have been reported using neurophysiological methods, such as EEG, to better understand the neural processes enhanced by exercise. These findings, from experimental studies in children and adults, include increased alpha (Brümmer, Schneider, Abel, Vogt, & Strüder, 2011; Mierau et al., 2014; Moraes et al., 2011; Schneider, Brümmer, Abel, Askew, & Strüder, 2009b; St-Louis-Deschenes, Moore, & Ellemberg, 2015a) and beta spectral power (Moraes et al., 2007, 2011; Schneider et al., 2009b), mainly in frontal and parietal areas, during resting-state conditions, which are thought to reflect arousal and activation. However, the direction of these effects on alpha and beta EEG power has been mixed and findings have been inconsistent (Brümmer et al., 2011; Mierau et al., 2014; Moraes et al., 2007; Schneider et al., 2009b; St-Louis-Deschenes et al., 2015a). Discrepancies in study findings are likely due to heterogeneity in study methodologies

and exercise paradigms, but also a lack of a control group in some studies (Fumoto et al., 2010; Mierau et al., 2014; Schneider et al., 2009b).

The most consistent ERP finding has been an exercise-induced increase in P3 amplitude in flanker and Go/No-go tasks during target stimulus presentation (Go P3), reflecting attention allocation and execution (Chang, Pesce, Chiang, Kuo, & Fong, 2015a; Drollette et al., 2014; Hillman, Snook, & Jerome, 2003; Kamijo et al., 2004; Kamijo, Nishihira, Higashiura, & Kuroiwa, 2007; St-Louis-Deschenes, Moore, & Ellemberg, 2015b). Enhancements in Go P3 amplitude after exercise have in some studies been paralleled with improved behavioural performance of faster reaction times (Kamijo et al., 2009, 2007; Ludyga et al., 2017), and increased performance accuracy (Drollette et al., 2014; Hillman, Kamijo, & Scudder, 2011). The literature on the effect of exercise on brain measures of specific cognitive processes is still limited and few studies have explored effects across several cognitive tasks and ERP components in a single testing session.

In Chapter 6 we aimed to investigate the effects of a single bout of high-intensity aerobic exercise on a cycle ergometer on a range of performance and EEG measures implicated in attention, inhibition and performance-monitoring. These measures were obtained across three successive cognitive tasks, performed 30 to 64 minutes after exercise, in a population sample of young adult men.

1.6.3 Summary

NICE guidelines recommend behavioural interventions as first-line treatment for children and adolescents with mild to moderate severity of ADHD symptoms, while pharmacotherapy can be used in combination with behavioural interventions as first-line treatment in cases with severe impairments or comorbid ODD/CD. Pharmacotherapy is used as first-line treatment for adults with ADHD. Meta-analytic evidence suggests that pharmacological medication is overall effective in treating core ADHD symptoms. Behavioural interventions have been found to be effective in treating parent and child functioning, but not core ADHD symptoms. Emerging

research has suggested beneficial effects of physical exercise on performance and brain-indices of cognitive processing in individuals with ADHD and in healthy populations, highlighting the potential role for exercise as a protective factor and treatment in ADHD.

1.7 Aims and objectives

This thesis aims to investigate informant source validity, genetic and neurobiological correlates of ADHD in adolescents and adults using a multi-disciplinary approach. In the first part of the thesis (Chapters 2 and 3), the aim is to evaluate the validity of informant sources for ADHD by examining associations with cognitive-neurophysiological correlates and future adverse life outcomes using both clinical and epidemiological samples. The second part of the thesis (Chapters 4, 5 and 6) aims to further our understanding of different aspects of biological factors associated with ADHD, using a combination of both clinical and population samples. Specifically, the aims are to (1) examine the genetic associations between ADHD and commonly co-occurring traits and disorders, (2) establish the stability of autonomic arousal profiles in ADHD, indexed by electrodermal activity, and (3) study the effects of physical exercise on cognitive-neurophysiological measures of attention, inhibition and performance-monitoring.

1.7.1 Informant source validity of ADHD in adolescents and young adults (Chapters 2 and 3)

In the first two data-based chapters, the studies aim to investigate the validity of self- and parent-report of ADHD in the transitional stage from childhood (where parent- and teacher-report are gold-standard for diagnosis) into young adulthood, where self-report becomes increasingly important for diagnosis, in both research and clinical settings.

In Chapter 2, the main aim is to evaluate the construct validity of self-reported ADHD by investigating how well self-report of symptoms and impairment is reflected by

cognitive-neurophysiological and movement measures, which have previously been well reflected by parent-reported ADHD in the same sample (Cheung et al., 2016). These analyses are conducted on a follow-up sample of children with ADHD diagnoses and controls when they reached adolescence and young adulthood (Sibling EEG Follow Up Study; SEFOS). The objective in Chapter 3 is to evaluate the predictive validity of self- and parent-rated ADHD symptoms across adolescence on future adverse life outcomes. In a population-based sample (Twin Study of Child and Adolescent Development; TCHAD), I examine how well self- and parent-rated symptoms in early (13-14 years) and late (16-17 years) adolescence can predict adverse socioeconomic and health outcomes in early adulthood, both by exploring the unadjusted associations and associations adjusted for the other informant.

The overarching aim of the research in these two chapters are to examine the validity of each informant using different, converging approaches, in the transitional age between childhood and adulthood. Understanding which informant source is the most valuable or insightful in a certain developmental stage can inform researchers and clinical practitioners about the source to prioritise during diagnosis in the age group.

1.7.2 Neurobiology and genetics in ADHD (Chapters 4, 5 and 6)

The second part of this thesis aims to elucidate different aspects of the biological underpinnings of ADHD, by employing genetic, electrodermal and cognitive-electrophysiological methods in population-based and clinical samples.

In Chapter 4, the objective is to examine whether the frequent co-occurrences of other traits and disorders in ADHD can be explained by common genetic factors, by using powerful PRSs derived from the newly available large-scale mega-GWAS. Specifically, associations are examined between PRSs for ADHD and several frequently co-occurring conditions in a large population-based sample (UK Biobank Resource). In Chapter 5, the main goal is to investigate if autonomic arousal, indexed by electrodermal activity, in individuals with ADHD changes over a long testing session and across time, to clarify if arousal profiles are context-dependent or reflect stable impairments. Using a clinical

sample (SEFOS), autonomic arousal profiles of individuals with ADHD are explored across a long testing assessment, consisting of four successive resting-state and task (CPT-OX and Fast Task) conditions. The main aim in Chapter 6 is to explore the effects of physical exercise, compared to rest, on cognitive-performance and EEG measures of attention, inhibition and conflict-monitoring. Cognitive-performance and EEG measures across three successive task conditions (CPT-OX, Flanker and Fast Tasks) are compared before and after a high-intensity exercise session and a resting control condition in young and healthy adult men (Effect of Physical Activity on Cognition and Brain Function; PHAB).

Overall, the second part of this thesis uses a multidisciplinary approach to investigate biological correlates in ADHD, to further our understanding of the underlying mechanisms underlying the disorder. The knowledge gained from this research will hopefully add to our understanding of the aetiology of ADHD - with long-term implications for treatment guidelines and improving diagnosis in clinical practice.

CHAPTER 2 – Self-report of ADHD shows limited agreement with objective markers of persistence and remittance

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Self-report of ADHD shows limited agreement with objective markers of persistence and remittance

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ABSTRACT

Objective: A controversial issue is whether self-report of symptoms and impairment is sufficient for diagnosis of attention-deficit/hyperactivity disorder (ADHD) in adolescents and adults in the absence of other informants, such as parents. The present study investigated how well self-report is reflected by cognitive-neurophysiological and actigraph measures, which we have previously shown to discriminate between ADHD persisters, remitters and controls using parent-report (Cheung et al., 2015; Brit J Psychiat http://dx.doi.org/10.1192/bjp.bp.114.145185).

Method: Parent- and self-reported ADHD symptoms and impairment, together with cognitive, electroencephalogram (EEG) frequency, event-related potential (ERP) and actigraph measures were obtained from 108 adolescents and young adults with childhood ADHD and 167 controls.

Results: Participants reported lower levels of ADHD symptoms and impairments than parents ($p < 0.05$) and the ADHD persistence rate based on self-report was low at 44%, compared to the persistence rate of 79% previously reported based on parent-report. Regression analyses showed that the objective measures distinguished poorly between ADHD persistent and remittent groups based on self-report, in contrast to findings based on parent-report (Cheung et al., 2015), although the measures differentiated well between ADHD persisters and controls. Correlation analyses revealed that self-reported impairment significantly correlated with fewer of the objective measures, despite parent- and self-reported symptoms showing similar correlations with the measures.

Conclusions: The findings show that self-reported ADHD outcome is not as well reflected by cognitive-neurophysiological and movement correlates as we previously found for parent-reported ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder that frequently has long-term impact throughout the lifespan (National Institute of Health and Clinical Excellence; NICE, 2008). Childhood ADHD has an estimated prevalence of around 5.3% (95% CI: 5.01–5.56) world-wide (Polanczyk et al., 2007), and often persists into adulthood where the prevalence rate is 2.5% (95% CI: 2.1–3.1) (Simon et al., 2009). While parents and teachers are used as main sources for establishing diagnoses in children, self-report becomes increasingly important during diagnostic interviews in adolescence and young adulthood. There is, however, scarcity of research evaluating the

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validity of self-report compared to informant-report in establishing diagnosis of ADHD in adolescents and young adults.

Previous research suggests modest agreement between self- and parent-ratings of ADHD symptoms in adolescents and young adults (r = 0.16–0.30) (Barkley et al., 2002; Pierrehumbert et al., 2006; Wan Salwina, 2013). Young individuals tend to report their ADHD symptoms as less severe than their parents, which results in lower rates of ADHD persistence into adulthood based on self-report (Barkley et al., 2002; Kooij et al., 2008; Pierrehumbert et al., 2006). This suggests that follow-up studies that rely on self-report may estimate persistence of ADHD to be lower than studies using parent-report (Barkley et al., 2002; Wolraich et al., 2005). The exclusive reliance on adult self-report may have in part contributed to the low ADHD persistence rate of 5% recently reported by Moffitt et al. (2015), which is substantially lower than previous follow-up studies that have relied on both self- and parent-report and reported persistence rates between 15% and 35% (Biederman et al., 2010; Faraone et al., 2006). This discrepancy could also be explained by differences between population and clinical samples.

Overall, existing research is limited, yet suggestive evidence is emerging that self-report of ADHD may have lower validity than parent-report. Population-based and clinical ADHD studies have found that self-reported ADHD symptoms show weaker associations with poor school achievement in adolescence (Pierrehumbert et al., 2006) and major life events in young adulthood (Barkley et al., 2002), compared to parent-report. Furthermore, the estimated heritability of adolescent and adult ADHD based on self-reported symptoms (38–48%) (Larsson et al., 2013; Merwood et al., 2013) is lower than heritability estimates based on parent-reported symptoms (64–82%) (Cheung et al., 2015; Merwood et al., 2013), and clinically-diagnosed ADHD (88%) (Larsson et al., 2014), as defined by taking ADHD medication. The low heritability estimates for self-reported ADHD could be attributed to rater-bias effects introduced by using self-report, but is also likely due to the use of different informants to rate each twin in a pair rather than relying on a single informant (Brikell et al., 2015; Merwood et al., 2013).

While studies converge in suggesting that self-report of ADHD shows lower validity than parent-report, no studies have compared the validity of source informants using cognitive-neurophysiological and movement correlates of ADHD. Objective measures could be used to examine how well each informant report of ADHD is reflected by cognitive-neurophysiological and movement data.

We previously reported findings from a prospective study that successfully discriminated between ADHD persistent, remittent and control groups on cognitive-electrophysiological and actigraph measures (Cheung et al., 2015). The ADHD groups were based on parent-reports, given the relatively young age range of the sample (11–25 years), as literature suggests children with ADHD may be poor at judging their own problematic behavior (Hoza et al., 2002, 2004). Preparation-vigilance processes (omission errors (OE), reaction time variability (RTV), contingent negative variation (CNV), delta activity), as well as IQ and actigraph count, were markers of remission in early adulthood. These processes distinguished between ADHD persisters and remitters, but not between ADHD remitters and controls.

We now examine ADHD persistence and remittance based on self-report in young adulthood using the same sample as our previous study (Cheung et al., 2015). The aim is to gain a better understanding of discrepancies between self- and parent-report and to investigate how well self-report is reflected by ADHD symptomology at the level of cognition, neurophysiology and movement. Given how ADHD is defined, we can examine inattentive, hyperactive and impulsive symptoms at an objective level of attention processes and fidgeting, although it is important to acknowledge that these are not regarded as gold-standard objective measures in the diagnostic process of ADHD and are limited to laboratory settings.

The main aims of the present study are to examine (i) whether self- and parent-report of ADHD differ in severity; (ii) how well the objective data discriminate between ADHD persisters, remitters and controls based on self-report of ADHD using DSM-IV criteria and (iii) the pattern of correlations between self-reported ADHD symptoms and impairments and the objective data.

Based on DSM-IV (The Diagnostic and Statistical Manual of Mental Disorders, 4th ed.), individuals are diagnosed with ADHD if they display at least six symptoms in either the inattentive or hyperactive-impulsive domains, and experience symptoms and impairment in at least two settings. In the revised DSM-5 criteria, individuals aged 17 or older only require the presence of five symptoms and the presence of symptoms in at least two settings, rather than impairments from symptoms in two settings. Thus, we run additional analyses to investigate whether the objective data discriminate better between ADHD groups, based on self-report, using the revised DSM-5 criteria of displaying at least 5 ADHD symptoms.

2. Method

2.1. Participants

The sample consists of 275 participants, followed-up on average 5.8 years (SD = 1.1) after initial assessments. At follow-up, participants were on average 18.0 years of age (age range: 11.1–25.9). 17 individuals were between 11 and 13 years, 79 individuals were between 14 and 16 years, 116 individuals were between 17 and 19 years and 63 individuals were 20 years and older. 108 participants had a diagnosis of DSM-IV combined type ADHD in childhood (9 sibling pairs, 90 singletons) and 167 were controls (74 sibling pairs, 19 singletons).

Participants with ADHD were initially recruited from ADHD clinics in south-east England (Kuntsi et al., 2010). Diagnosis of DSM-IV combined type ADHD was established using the Parental Account of Childhood symptoms (PACS), a semi-structured interview with high inter-rater reliability (Chen et al., 2008). Controls were recruited from schools in the same region and were age and sex matched with the clinical sample. All participants were aged between 6 and 17 at initial assessment. Exclusion criteria were: IQ < 70, autism, epilepsy, general learning difficulties, brain disorders and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed by an appropriate ethical committee and informed consent of participants was obtained after the nature of the procedures had been fully explained.

At follow up, eight controls met ADHD criteria based on self- (n = 2) or parent- (n = 6) ratings on the Barkley Informant Rating Scale, and eight participants had missing self- or parent-ratings of impairments. These participants were excluded from analyses.

2.2. Procedure

Participants were scheduled for a follow-up clinical interview and cognitive-electroencephalogram (EEG) assessments at the research center where initial assessments took place. A 48-h ADHD medication-free period was required. The total length of the test session, including breaks, was approximately 4 h.

2.3. Measures

The Diagnostic Interview for ADHD in adults (DIVA) is a semi-structured interview evaluating the DSM-IV criteria for adult and childhood ADHD symptoms and impairment (Kooij and Francken, 2007). The DIVA was conducted by trained researchers with participants and parents separately.

The Barkley's functional impairment scale (BFIS) (Barkley and Murphy, 2006). This 10-item scale assesses levels of functional impairments associated with ADHD symptoms in five areas: family/relationship; work/education; social interaction; leisure activities and management of daily responsibilities. Each item ranged from 0 (never or rarely) to 3 (very often). Participants and parents both completed the questionnaire.

Participants were classified as ADHD persistent at follow-up based on DSM-IV criteria; if they scored 'yes' on $\geq$ 6 items in either the inattention or hyperactivity-impulsivity domains, and if they scored $\geq$2 on two or more areas of impairments.

Barkley Informant Rating Scale (Barkley and Murphy, 2006). This rating scale (based on DSM-IV items) was used to identify controls meeting ADHD diagnostic criteria at follow up. Each item ranged from 0 (never or rarely) to 3 (very often). Participants and parents both completed the questionnaire.

IQ and digit span. The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) were administered to derive an IQ estimate (Wechsler, 1999). The digit span subtest from the WISC-III (Wechsler, 1991) or the WAIS-III (Wechsler, 1997) was administered to participants aged below 16 and aged 16 or above, respectively, to obtain digit span forward (DSF) and backward (DSB). DSF requires participants to verbally repeat a sequence of digits in straightforward order, and measures short-term verbal memory. DSB requires participants to repeat digits in backward order, and measures verbal working memory.

Actigraph measures of activity level. Actigraph readings were taken during interviews and assessments. We previously showed that mean intensity and mean number of movements, obtained from the dominant ankle, reliably distinguished between ADHD probands and controls (ROC-AUC = 0.61–0.79) (Wood et al., 2009).

The Fast Task (Andreou et al., 2007). The baseline condition consists of 72 trials, which followed a standard warned four-choice RT task. Four empty circles (warning signals, arranged horizontally) first appeared for 8s, after which one of them (the target) was colored in. Participants were asked to press the response key corresponding to the target position. Following responses, the stimuli disappeared and a fixed inter-trial interval of 2.5s followed. Speed and accuracy were emphasized equally. If participants did not respond within 10s, the trial terminated. A comparison condition with a fast event rate (1s) and incentives followed the baseline condition. We used the RTV from the baseline condition, as this condition is more sensitive to ADHD (Kuntsi et al., 2013).

The cued flanker Continuous Performance Task (CPT-OX) (Doehnert et al., 2008; Valko et al., 2009). This CPT includes rare cued Go and NoGo conditions embedded in a vigilance task with frequent distractors to assess attention and inhibition. 400 letters are presented for 150 ms with a stimulus onset asynchrony of 1.65 s in a pseudo-randomized order. The cue letter O occurred with 20% probability (80 Cue stimuli), signaling a Go–NoGo task. Participants pressed a button as fast as possible every time the cue was followed directly by the letter X (O-X) target sequence (10% probability, 40 Go stimuli), but had to withhold responses to O-not-X sequences (NoGo trials, also 10%, 40 NoGo stimuli). RTV, commission errors (CE), OE; EEG frequency bands; and event-related potential (ERP) amplitude measures of CNV, cue-P3 and nogo-P3 were obtained.

2.4. EEG recording and processing

EEG was recorded from 62 channels DC-coupled recording system (extended 10–20 montage), with a 500 Hz sampling-rate, impedances kept under 10 kΩ and FCz as the reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi.

The EEG data were analyzed using Brain Vision Analyzer (2.0) (Brain Products, Munich, Germany). After down-sampling the data to 256 Hz, the EEG data were re-referenced to the average and filtered offline with digitally band-pass (0.1–30 Hz, 24 dB/oct) Butterworth filters. Ocular artifacts were identified using Independent Component Analysis (ICA) (Jung et al., 2000). The extracted components were manually inspected and ocular artifacts were removed by back-projection of all but those components. Data with other artifacts exceeding ±100 μV in any channel were rejected. No baseline subtraction was applied in line with previous ERP analyses on this task (Doehnert et al., 2013; McLoughlin et al., 2011). All averages contained at least 20 sweeps.

2.5. ERP analyses

The CNVs were analyzed as mean amplitudes 1300–1650ms following cues over the central electrode (Cz). The cue-P3 had a parietal maximum and was defined as the most positive peak 250–600ms following cue trials at electrode Pz. The nogo-P3 was defined as the most positive peak 250–600ms following no-go trials at electrode Cz.

2.6. EEG frequency analyses

We estimated mean EEG power (μV^2) by computing the mean activity of electrodes (F1–F8, Fz) in the delta (0.5–3 Hz), theta (4–7 Hz), alpha (7–12 Hz) and beta (12–30 Hz) bands using the Fast Fourier Transform (FFT). We analyzed the frontal location only, to be consistent with our previous analyses (Cheung et al., 2015).

2.7. Statistical analyses

We ran regression models with dummy variables to identify which measures showed an effect of group (ADHD persisters vs ADHD remitters vs controls), with controls as the reference group. Post-hoc *t*-tests were conducted to examine ADHD persistent-remittent differences. We explored the effect of sex by re-running analyses with females (n = 55) removed. We also re-ran the analyses using groups based on DSM-5 criteria of having five, rather than six, ADHD symptoms. Cohen's *d* effect sizes are presented with means, SDs and test statistics for the group analyses; 0.2 is considered a small effect, 0.5 a medium effect and 0.8 a large effect.

Pearson correlations were conducted on the objective measures to examine their associations with DIVA ADHD symptom scores and clinical impairment, within those with childhood ADHD, with age and gender included as covariates.

We ran additional analyses to investigate whether the combination of information from self- and parent-reports is better reflected by the objective measures compared to only using parent-report. We compared profiles of individuals with both self- and parent-reported ADHD (concordant group), individuals with only parent-reported ADHD (discordant group) and controls on the objective measures and reports of impairment. We did not examine individuals with only self-reported ADHD as this group of individuals was too small (n = 17).

We re-ran all analyses covarying for IQ to examine its potential effects. All cognitive and EEG measures were skewed and log-transformed to normal in STATA version 10 (StataCorp, College

Station, TX). Genetic relatedness between the sibling pairs was controlled for by using the 'robust cluster' command in STATA.

3. Results

Based on self-reports of symptoms and impairment, 44% of individuals with childhood ADHD continued to meet DSM-IV levels of ADHD and were classified as ADHD persisters. As reported previously (Cheung et al., 2015), 79% of individuals were classified as ADHD persisters based on parent-report. Using DSM-5 symptom criteria, 47% of individuals were classified as ADHD persisters based on self-report, while the persistence rate remained the same for parent-report.

At follow up, based on self-report, ADHD persisters, remitters and controls did not differ in age, but there were significantly more males in the remitted group than the control group (Table 1). The

Table 1
Comparisons on age, sex, IQ, digit span, cognitive, event-related potential (ERP), electroencephalogram (EEG) and actigraph measures between ADHD groups based on self-report.

	ADHD persisters (n = 48)	ADHD remitters (n = 60)	Controls (n = 167)	*F*	*df*	*p*	*Cohen's d'*	*Cohen's d' (IQ controlled)*
Mean age (SD)	18.54 (2.89)	18.34 (3.19)	17.77 (2.20)	1.94	2, 191	0.15		
Male *n (%)*	39 (81%)	54 (90%)	127 (76%)	4.07	2, 191	**0.02**		
Cognitive measures								
IQ	98.25 (17.06)	97.20 (13.86)	110.23 (12.15)	21.76	2, 191	**<0.01**	[a] = −0.58**	
							[b] = 0.07	
							[c] = −0.80**	
Digit span forward	9.60 (2.45)	9.38 (1.74)	10.46 (2.15)	7.46	2, 190	**<0.01**	[a] = −0.31*	[a] = −0.09
							[b] = 0.10	[b] = 0.06
							[c] = −0.51**	[c] = −0.17
Digit span backward	6.17 (2.37)	6.62 (2.42)	8.04 (2.61)	12.34	2, 190	**<0.01**	[a] = −0.61**	[a] = −0.38*
							[b] = −0.19	[b] = −0.27
							[c] = −0.51**	[c] = −0.16
RTV (CPT-OX)	99.55 (51.97)	107.00 (60.77)	79.05 (36.96)	5.82	2, 190	**<0.01**	[a] = 0.34*	[a] = 0.21
							[b] = −0.07	[b] = −0.05
							[c] = 0.39**	[c] = 0.26
RTV (Fast Task)	4.77 (0.77)	4.37 (0.86)	3.76 (0.89)	28.67	2, 191	**<0.01**	[a] = 0.99**	[a] = 0.80**
							[b] = 0.50**	[b] = 0.58**
							[c] = 0.59**	[c] = 0.36**
CE (CPT-OX)	1.96 (2.44)	1.98 (2.37)	0.86 (1.33)	10.04	2, 190	**<0.01**	[a] = 0.40**	[a] = 0.29*
							[b] = −0.06	[b] = −0.04
							[c] = 0.52**	[c] = 0.32*
OE (CPT-OX)	2.79 (3.76)	2.01 (3.78)	0.60 (1.00)	14.00	2, 189	**<0.01**	[a] = 0.61**	[a] = 0.52**
							[b] = 0.34	[b] = 0.38
							[c] = 0.44**	[c] = 0.22
ERPs (CPT-OX)								
CNV	−2.76 (1.80)	−3.21 (1.83)	−3.84 (1.86)	6.75	2, 187	**<0.01**	[a] = 0.47**	[a] = 0.43**
							[b] = 0.25	[b] = 0.25
							[c] = 0.28*	[c] = 0.21
Cue P3	6.51 (0.50)	6.71 (0.56)	6.81 (0.44)	6.86	2, 187	**<0.01**	[a] = −0.50**	[a] = −0.51**
							[b] = −0.38	[b] = −0.38
							[c] = −0.19	[c] = −0.18
No-go P3	7.00 (0.46)	7.06 (0.36)	7.17 (0.38)	3.33	2, 179	**0.04**	[a] = −0.30*	[a] = −0.23
							[b] = −0.13	[b] = −0.13
							[c] = −0.26	[c] = −0.16
EEG frequency bands (CPT-OX)								
Delta	1.54 (0.49)	1.58 (0.54)	1.45 (0.43)	1.58	2, 188	0.21	[a] = 0.16	[a] = −0.03
							[b] = −0.08	[b] = −0.07
							[c] = 0.22	[c] = 0.03
Theta	−0.15 (0.53)	−0.15 (0.55)	−0.25 (0.51)	1.60	2, 188	0.20	[a] = 0.19	[a] = 0.03
							[b] = −0.08	[b] = 0.01
							[c] = 0.20	[c] = 0.03
Alpha	−0.35 (0.62)	−0.41 (0.72)	−0.59 (0.61)	3.43	2, 189	**0.03**	[a] = 0.33*	[a] = 0.26
							[b] = 0.10	[b] = 0.10
							[c] = 0.22	[c] = 0.16
Beta	−1.65 (0.69)	−1.63 (0.54)	−1.80 (0.57)	2.24	2, 189	0.11	[a] = 0.18	[a] = 0.10
							[b] = −0.04	[b] = −0.03
							[c] = 0.27	[c] = 0.15
Actigraph movement								
Mean intensity	1.20 (0.74)	1.03 (0.69)	0.77 (0.55)	7.83	2, 168	**<0.01**	[a] = 0.54**	[a] = 0.45**
							[b] = 0.25	[b] = 0.26
							[c] = 0.34*	[c] = 0.25
Mean count	0.05 (0.04)	0.04 (0.04)	0.03 (0.06)	5.82	2, 141	**<0.01**	[a] = 0.42**	[a] = 0.33*
							[b] = 0.26	[b] = 0.25
							[c] = 0.27	[c] = 0.19

RTV, reaction time variability; CE, commission errors; OE, omission errors; CNV, continuous negative variation *p-value < 0.05, ** p-value < 0.01. P-values presented in bold are significant.
[a] ADHD persisters vs controls.
[b] ADHD persisters vs ADHD remitters.
[c] ADHD remitters vs controls.

follow-up duration was not significantly different between persistent and remittent groups ($z = 0.31$, $p = 0.76$).

Almost half (47%) of the participants were under medication treatment for ADHD at the time of the follow-up assessment. The proportion of participants on medication at follow up did not differ between persistent and remittent groups based on either self-report ($\chi = 1.46$, $p = 0.23$) or parent-report ($\chi = 1.95$, $p = 0.16$).

3.1. Do self-reports of ADHD symptoms and impairments differ in severity from parent-reports in individuals with a childhood diagnosis of ADHD?

The average number of self-reported inattentive symptoms ($M = 5.82$, $SD = 0.23$) was significantly lower ($t(107) = 6.85$, $p < 0.001$) than the number of parent-reported symptoms

Table 2
Comparisons on age, sex, IQ, digit span, cognitive, event-related potential (ERP), electroencephalogram (EEG) and actigraph measure between ADHD groups based on self-report using DSM-5 criteria.

	ADHD persisters (n = 51)	ADHD remitters (n = 57)	Controls (n = 167)	*F*	*df*	*p*	*Cohen's d'*
Mean age (SD)	18.55 (2.81)	18.32 (3.27)	17.77 (2.20)	2.03	2, 191	0.13	
Male *n (%)*	42 (82%)	51 (89%)	127 (76%)	3.59	2, 191	**0.03**	
Cognitive measures							
IQ	98.29 (16.58)	97.11 (14.18)	110.23 (12.15)	21.41	2, 191	**<0.01**	[a] = −0.61** [b] = 0.08 [c] = −0.79**
Digit span forward	9.64 (2.39)	9.33 (1.76)	10.46 (2.15)	7.72	2, 190	**<0.01**	[a] = −0.30* [b] = 0.15 [c] = −0.51**
Digit span backward	6.18 (2.31)	6.63 (2.45)	8.04 (2.61)	12.50	2, 190	**<0.01**	[a] = −0.62** [b] = −0.19 [c] = −0.48**
RTV (CPT-OX)	96.62 (51.76)	109.96 (60.88)	79.05 (36.96)	6.08	2, 190	**<0.01**	[a] = 0.29* [b] = −0.19 [c] = 0.43**
RTV (Fast Task)	4.78 (0.89)	4.39 (0.86)	3.76 (0.89)	26.43	2, 191	**<0.01**	[a] = 0.94** [b] = 0.40* [c] = 0.59**
CE (CPT-OX)	1.86 (2.63)	2.07 (2.40)	0.86 (1.33)	10.33	2, 190	**<0.01**	[a] = 0.37** [b] = −0.15 [c] = 0.54**
OE (CPT-OX)	2.60 (3.72)	2.11 (3.86)	0.60 (1.00)	13.59	2, 189	**<0.01**	[a] = 0.60** [b] = 0.26 [c] = 0.45**
ERPs (CPT-OX)							
CNV	−2.90 (1.91)	−3.11 (1.74)	−3.84 (1.86)	5.92	2, 187	**<0.01**	[a] = 0.40** [b] = 0.11 [c] = 0.33*
Cue P3	6.55 (0.51)	6.69 (0.56)	6.81 (0.44)	6.36	2, 187	**<0.01**	[a] = −0.45** [b] = −0.22 [c] = −0.26
No-go P3	7.00 (0.50)	6.99 (0.45)	7.17 (0.38)	3.33	2, 179	**0.04**	[a] = −0.26 [b] = −0.03 [c] = −0.29*
EEG frequency bands (CPT-OX)							
Delta	1.54 (0.54)	1.61 (0.54)	1.45 (0.43)	1.88	2, 188	0.16	[a] = 0.11 [b] = −0.20 [c] = 0.26
Theta	−0.17 (0.53)	−0.09 (0.61)	−0.25 (0.51)	1.66	2, 188	0.19	[a] = 0.16 [b] = −0.10 [c] = 0.23
Alpha	−0.37 (0.61)	−0.40 (0.73)	−0.59 (0.61)	3.22	2, 189	**0.04**	[a] = 0.31* [b] = 0.04 [c] = 0.23
Beta	−1.68 (0.68)	−1.60 (0.54)	−1.80 (0.57)	2.69	2, 189	0.07	[a] = 0.15 [b] = −0.13 [c] = 0.31*
Actigraph movement							
Mean intensity	1.15 (0.75)	1.06 (0.68)	0.77 (0.55)	7.44	2, 168	**<0.01**	[a] = 0.49** [b] = 0.14 [c] = 0.37*
Mean count	0.05 (0.04)	0.04 (0.04)	0.03 (0.06)	5.71	2, 141	**<0.01**	[a] = 0.48** [b] = 0.25 [c] = 0.32*

RTV, reaction time variability; CE, commission errors; OE, omission errors; CNV, continuous negative variation * p-value < 0.05, ** p-value < 0.01. P-values presented in bold are significant.
[a] ADHD persisters vs controls.
[b] ADHD persisters vs ADHD remitters.
[c] ADHD remitters vs controls.

(M = 7.44, SD = 0.19). Self-reported hyperactive-impulsive symptoms (M = 4.86, SD = 0.23) was significantly lower (t (107) = 3.54, p < 0.001) than parent-reported hyperactive-impulsive symptoms (M = 5.84, SD = 0.25). Self-reported impairment was significantly lower (t (105) = 4.67, p < 0.001) for self-report (M = 11.01, SD = 5.73) than parent-report (M = 13.91, SD = 6.64). There was a significant correlation between self- and parent-reported ADHD symptoms (r = 0.37, p < 0.001), as well as impairments (r = 0.48, p < 0.001).

3.2. Which processes are impaired in the ADHD persistent group based on self-report?

ADHD persistent-control group differences were observed on all measures except for EEG delta, theta and beta activity, and movement count (p > 0.05). After controlling for IQ, there were no longer significant ADHD persistent-control differences on DSF, RTV (from CPT-OX) and alpha activity (Table 1). Controlling for IQ led to slight reductions in effect sizes for most variables; however, the effect size was still large for RTV from Fast Task (Table 1). When we re-ran the analyses excluding females, the pattern of findings did not change.

3.3. Which processes are impaired in the ADHD remittent group defined by self-report?

ADHD remittent-control group differences were observed on the same measures that distinguished ADHD persisters from controls, except for cue-P3. After controlling for IQ, ADHD remittent-control group differences remained only for RTV (Fast Task), CE and OE, and the effect sizes were reduced (Table 1).

When we re-ran the analyses with females removed a significant ADHD remittent-control difference in EEG beta activity emerged, and there were no longer significant differences on CNV and DSF between remitters and controls (p > 0.05). The results did not change for the remaining variables.

3.4. Which processes are markers of remission that distinguish between ADHD persistent and remittent groups defined by self-report?

A marker of remission refers to a measure that distinguishes ADHD remitters from persisters, but not from controls. In this study, ADHD persisters and remitters only significantly differed on RTV (Fast Task). However, as the measure also distinguished ADHD remitters from controls (p < 0.05) (Table 1), it does not fulfill the criteria as a marker of remission but rather represents an intermediate deficit in ADHD remitters. After controlling for IQ, the group ADHD persistent-remittent group difference remained significant for RTV (p < 0.001) and the effect size increased slightly (from d' = 0.54 to d' = 0.61). The pattern of results did not change when analyses excluded females.

3.5. How well do the objective data discriminate between ADHD groups based on DSM-5 diagnostic symptom criterion?

When ADHD status was based on self-reports using the DSM-5 symptom criterion of 5 rather than 6 symptoms, three individuals were re-classified as ADHD persisters, from being ADHD remitters according to DSM-IV. The group-based analyses based on DSM-5 criteria showed the same results as when groups were based on DSM-IV criteria, with the exceptions that significant ADHD remittent-control group differences emerged on the nogo-P3, intensity movement count and beta activity, and there was no longer a significant ADHD persistent-control group difference on nogo-P3 (Table 2).

When ADHD groups were based on parent-reports using the DSM-5 criterion, the same individuals were classified as ADHD persisters and remitters as when DSM-IV criteria were used.

Table 3
Pearson correlations (two-tailed) of IQ, digit span, cognitive, event-related potential (ERP), electroencephalogram (EEG) and actigraph measures with self-reported symptoms and impairment in individuals with childhood ADHD (N = 108).

	ADHD symptoms		Impairment	
	r	*p*	*r*	*p*
IQ	−0.12	0.21	0.02	0.81
Digit span forward	0.02	0.83	−0.02	0.83
Digit span backward	−0.07	0.45	−0.01	0.92
RTV (CPT-OX)	**0.23**	**0.02**	0.02	0.82
RTV (Fast Task)	**0.33**	**<0.01**	**0.21**	**0.03**
Commission errors	−0.01	0.94	0.04	0.70
Omission errors	**0.24**	**0.01**	0.18	0.07
CNV	0.18	0.07	0.06	0.53
Cue P3	−0.14	0.15	**−0.19**	**0.05**
No Go P3	−0.01	0.93	0.03	0.75
Delta	**0.21**	**0.03**	−0.01	0.89
Theta	**0.21**	**0.04**	0.01	0.91
Alpha	**0.19**	**0.04**	0.14	0.16
Beta	0.09	0.37	0.09	0.35
Movement intensity	0.18	0.09	0.06	0.60
Movement count	**0.26**	**0.03**	0.18	0.15

RTV, reaction time variability; CE, commission errors; OE, omission errors; CNV, continuous negative variation. Significant values are presented in bold.

3.6. Which objective measures are associated with the continuous ratings of self-reported ADHD symptoms and impairments at follow up in individuals with childhood ADHD?

Self-reported ADHD symptoms at follow up correlated significantly with RTV (CPT-OX & Fast Task), OE, delta, theta and alpha activity and movement count. Self-reported ADHD impairment correlated significantly only with RTV (Fast Task) and cue-P3 amplitude (Table 3). After controlling for IQ, all significant correlations remained significant, with only slight or no reduction in coefficient magnitudes (Table 4).

Table 4
Pearson correlations of IQ, digit span, cognitive, event-related potential (ERP), electroencephalogram (EEG) and actigraph measures with self-reported symptoms and clinical impairment in individuals with childhood ADHD (N = 108); controlling for IQ.

	ADHD symptoms		Impairment	
	r	*p*	*r*	*p*
Digit span forward	0.07	0.49	−0.03	0.76
Digit span backward	−0.03	0.75	−0.02	0.84
RTV (CPT-OX)	**0.21**	**0.03**	0.02	0.83
RTV (Fast Task)	**0.31**	**<0.01**	**0.23**	**0.03**
Commission errors	−0.04	0.69	0.05	0.64
Omission errors	**0.22**	**0.02**	0.19	0.06
CNV	0.17	0.09	0.06	0.62
Cue P3	−0.13	0.20	**−0.20**	**0.05**
No Go P3	<0.01	0.96	0.03	0.75
Delta	0.19	0.06	−0.01	0.89
Theta	**0.19**	**0.05**	0.01	0.89
Alpha	**0.19**	**0.05**	0.14	0.16
Beta	0.09	0.35	0.09	0.35
Movement intensity	0.17	0.11	0.05	0.64
Movement count	**0.26**	**0.04**	0.17	0.19

RTV, reaction time variability; CE, commission errors; OE, omission errors; CNV, continuous negative variation. Significant values are presented in bold.

3.7. Concordant versus discordant diagnostic groups according to self- and parent-report

The concordant ADHD group (meeting ADHD criteria according to both informant reports) and discordant group (meeting ADHD criteria according to parent report only) both significantly differed from controls and not from each other on: IQ and twelve objective measures, including digit span (backward & forward), RTV (Fast Task & CPT-OX), CE, OE, No-go P3, CNV, alpha activity and movement intensity (Table 5). The pattern of results remained the same after controlling for IQ in that no measure significantly differentiated between the concordant and discordant groups. All groups significantly differed from each other on self- and parent-reported functional impairment, with the concordant group showing the highest levels of reported impairment and controls showing the lowest levels of reported impairment.

4. Discussion

Our follow-up study of 108 adolescents and young adults with a childhood ADHD diagnosis and 167 controls revealed that ADHD persistence and remittance based on self-report is poorly differentiated by the objective measures, as opposed to groups defined by parent-report (Cheung et al., 2015). Although individuals with persistent ADHD showed impairments relative to controls on most objective measures, the objective measures did not differentiate well between ADHD persisters and remitters. Overall, individuals with childhood ADHD rated their levels of symptoms and impairments as less severe than parents, leading to markedly different prevalence rates of ADHD depending on rater. These findings suggest that: (1) adolescents and young adults with ADHD tend to report their levels of symptoms and impairments as lower than their parents; (2) prevalence rates vary markedly according to informant source; and (3) adolescents and young adults' reports of ADHD outcome are not as well reflected by objective cognitive, neurophysiological and movement measures as parent-reports.

Individuals with persistent ADHD showed significant impairments on nearly all objective measures, suggesting that ADHD persisters defined by self-report show similar profiles to ADHD persisters defined by parent-report. However, individuals who reported themselves as ADHD remittent showed similar profiles of underlying impairments as individuals who reported themselves as persistent. In contrast, when ADHD outcome was based on parent-reports (Cheung et al., 2015), ADHD persisters were impaired on all objective measures, while remitters did not differ from controls on any measures. ADHD remitters based on parent-reports differed from ADHD persisters but not controls on several measures, suggesting that these were markers of remission. Thus, the objective data was far better at distinguishing between persistent and remittent groups when these were based on parent-report, compared to self-report. These findings were similar when the revised DSM-5 symptom criteria for ADHD were applied to classify diagnostic status at follow-up. Furthermore, the concordant (meeting ADHD criteria according to both informant reports) and discordant (meeting ADHD criteria according to parent report only) groups significantly differed from controls on most measures and did not differ from each other on any objective measure, suggesting that self-reports of ADHD at follow-up added little value over and above parent-report alone in the association of ADHD with the objective measures studied.

The analyses on continuous measures of ADHD symptoms revealed that self- and parent-reports showed similar patterns of associations with the objective measures, suggesting a quantitative difference between self- and parent-reported symptoms, as they differed in mean severity. Self-reported impairment correlated significantly with fewer objective measures than parent-reported impairment, suggesting a qualitative difference between the informants despite the moderately strong correlation ($r = 0.48$, $p < 0.001$) between them. This suggests that individuals evaluate their level of impairment based on other factors than their parents. Further investigations into self-reported impairment and its correlates would be beneficial in order to understand on what basis young individuals estimate their levels of impairment.

It is important to acknowledge that there were notable discrepancies in results depending on which informant was used. The ADHD persistence rate based on self-reports was almost half the

Table 5
Comparison on objective measures and reports of impairments between ADHD concordant and discordant groups and controls.

	Controls (n = 167)	Concordant ADHD group (n = 43)	Discordant ADHD group (n = 42) (only parent-reported ADHD)
Age	17.77 (2.20)	18.45 (2.90)	18.16 (3.23)
Male n (%)	127[c]	34	36[a]
IQ	110.23 (12.15)[b,c]	97.35 (17.23)[a]	94.21 (12.96)[a]
DSF	10.46 (2.15)[b,c]	9.26 (2.36)[a]	9.33 (1.65)[a]
DSB	8.04 (2.61)[b,c]	5.98 (2.36)[a]	6.48 (2.45)[a]
RTV (CPT-OX)	79.05 (36.96)[b,c]	99.02 (47.56)[a]	122.81 (63.26)[a]
RTV (Fast Task)	3.76 (0.89)[b,c]	4.86 (0.90)[a]	4.59 (0.77)[a]
CE	0.86 (1.33)[b,c]	2.05 (2.74)[a]	2.17 (2.47)[a]
OE	0.60 (1.00)[b,c]	2.95 (3.87)[a]	2.64 (4.36)[a]
Cue P3	6.81 (0.44)[b]	6.52 (0.52)[a]	6.63 (0.56)
No-go P3	7.17 (0.38)[b,c]	6.99 (0.51)[a]	6.94 (0.48)[a]
CNV	−3.84 (1.86)[b,c]	−2.80 (1.87)[a]	−2.81 (1.75)[a]
Delta	1.45 (0.43)[c]	1.59 (0.54)	1.68 (0.56)[a]
Theta	−0.25 (0.51)[c]	−0.14 (0.55)	−0.02 (0.65)[a]
Alpha	−0.59 (0.61)[b,c]	−0.37 (0.64)[a]	−0.33 (0.77)[a]
Beta	−1.80 (0.57)[c]	−1.67 (0.66)	−1.56 (0.54)[a]
Actigraph intensity	0.77 (0.55)[b,c]	1.27 (0.76)[a]	1.11 (0.72)[a]
Actigraph count	0.03 (0.06)[b]	0.05 (0.04)[a]	0.05 (0.04)
Parent-reported impairment	2.73 (3.32)[b,c]	17.44 (4.97)[a,c]	15.26 (5.49)[a,b]
Self-reported impairment	3.29 (3.14)[b,c]	15.56 (4.46)[a,c]	8.08 (4.20)[a,b]

Concordant group: meeting ADHD criteria according to both self- and parent-report.
Discordant group: meeting ADHD criteria according to parent-report only.
[a] Significantly ($p < 0.05$) different from controls.
[b] Significantly ($p < 0.05$) different from concordant ADHD group.
[c] Significantly ($p < 0.05$) different from discordant ADHD group.

persistence rate based on parent-report. Furthermore, whereas several markers of remission were identified when ADHD status was based on parent-reports (Cheung et al., 2015), no markers of remission were identified using self-report. These discrepancies highlight the need for researchers to acknowledge differences in findings due to informant source used, which may explain inconsistencies in the ADHD literature across studies using different informants to measure ADHD.

Taken together with other research showing rater effects on ADHD prevalence rate at follow-up (Barkley et al., 2002) and heritability estimates (Merwood et al., 2013), further research is needed to clarify which rater is most valid. Based on the available data we would argue that parent ratings continue to be important in adolescence and young adulthood, as they appear to better reflect objective measures of impairment, as well as measures such as the heritability of ADHD. These findings may be particularly pertinent to recent publications suggesting that ADHD persistence rate in adults is very low (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015), as these are based on self reports.

A limitation of this study is the wide age range of the sample. Although age was controlled for in the quantitative analyses and there were no significant group differences on age, it would be important to investigate the validity of self- vs parent-report using a narrower age group, in particular individuals in their transition into young adulthood. Furthermore, only cases diagnosed with ADHD combined type in childhood were included in the sample in order to reduce heterogeneity in the sample. Thus, findings may not generalize to other presentations of ADHD. Moreover, we acknowledge that the term 'remitters', when based on self-reports, does not necessarily reflect a group of individuals who have remitted from self-reported ADHD, as self-reports were not obtained in childhood. Furthermore, although we found that self-report of ADHD outcome was not well reflected by objective measures, it is possible that self-report is better captured by other measures not included in our study.

In summary, this is the first study to suggest that self-report of ADHD outcome in adolescents and young adults is not as well reflected by cognitive-neurophysiological and movement data as parent-report. Our findings also demonstrate that there can be considerable inconsistencies in research findings based on the informant source used, which is important for researchers to acknowledge. For clinicians the findings suggest that during the follow-up of children with ADHD, care should be taken to continue to gather reports from multiple informants including parents.

Contribution disclosure

Ebba Du Rietz was involved in forming the research questions, executed the statistical analyses and wrote up the report. Dr Celeste Cheung contributed to the planning of the study design, collected the data and provided support during analysis and writing of the report. Professor Jonna Kuntsi played a key role in planning the study design and research questions, and provided input for interpretation of results and the write up of the report. Professor Philip Asherson also contributed with his input regarding the research questions, interpretation of results and writing of the report. Dr Grianne McLoughlin, Professor Daniel Brandeis and Professor Banaschewski contributed by giving input on data interpretation and on the writing of the report. All authors have approved the final article.

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Conflict of interest

Professor Banaschewski has served as adviser or consultant for Bristol Myers-Squibb, Develco Pharma, Lilly, Medice, Novartis, Shire, and Vifor Pharma; he has received conference attendance support and conference support or speakers honoraria from Janssen McNeil, Lilly, Medice, Novartis, and Shire and has been involved in clinical trials conducted by Lilly and Shire. Professor Asherson has acted in an advisory role for Shire, Janssen-Cilag, Eli-Lilly and Flynn Pharma. He has received education or research grants from Shire, Janssen-Cilag and Eli-Lilly. He has given talks at educational events sponsored by the above companies. Ebba Du Rietz, Dr Celeste Cheung, Dr Grainne McLoughlin, Professor Dr Daniel Brandeis and Professor Jonna Kuntsi report no biomedical financial interests or potential conflicts of interest.

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CHAPTER 3 – Predictive validity of parent- and self-rated ADHD symptoms in adolescence on adverse socioeconomic and health outcomes

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ORIGINAL CONTRIBUTION

Predictive validity of parent- and self-rated ADHD symptoms in adolescence on adverse socioeconomic and health outcomes

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Abstract There is scarcity of research investigating the validity of self-report of attention deficit hyperactivity disorder (ADHD) symptoms compared to other informants, such as parents. This study aimed to compare the predictive associations of ADHD symptoms rated by parents and their children across adolescence on a range of adverse socioeconomic and health outcomes in early adulthood. Parent- and self-rated ADHD symptoms were assessed in 2960 individuals in early (13–14 years) and late adolescence (16–17 years). Logistic regression analyses were used to compare the associations between parent- and self-rated ADHD symptoms at both time points and adverse life outcomes in young adulthood obtained from Swedish national registries. Both parent- and self-ratings of ADHD symptoms were associated with increased risk for adverse outcomes, although associations of parent-ratings were more often statistically significant and were generally stronger (OR = 1.12–1.49, $p < 0.05$) than self-ratings (OR = 1.07–1.17, $p < 0.05$). After controlling for the other informant, parent-ratings of ADHD symptoms in both early and late adolescence significantly predicted academic and occupational failure, criminal convictions and traffic-related injuries, while self-ratings of ADHD symptoms only in late adolescence predicted substance use disorder and academic failure. Our findings suggest that both parent- and self-ratings of ADHD symptoms in adolescence provides valuable information on risk of future adverse socioeconomic and health outcomes, however, self-ratings are not valuable once parent-ratings have been taken into account in predicting most outcomes. Thus, clinicians and researchers should prioritize parent-ratings over self-ratings.

Keywords ADHD · Developmental epidemiology · Rating scale · Validity

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that can have debilitating effects on individuals throughout the lifespan. Clinical and population-based studies have repeatedly shown that both ADHD diagnoses and elevated ADHD symptoms are associated with increased risk of experiencing serious life outcomes, such as educational and occupational difficulties, traffic injuries, criminal convictions and other psychiatric disorders [1–5]. Developing more effective ways of identifying individuals at risk for these serious life events later in life is important to prevent these adverse outcomes from occurring.

Childhood ADHD has an estimated prevalence of 5.3% (95% CI: 5.0–5.6%) worldwide and often persists into adulthood where the prevalence rate is around 2.5% (95% CI: 2.1–3.1%) [6, 7]. While parents and teachers are used

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as main sources for establishing diagnoses in children, self-report becomes increasingly important during diagnostic interviews in adolescence and young adulthood in both clinical and research settings.

There is scarcity of research that has studied how well parent- and self-ratings of ADHD symptoms in adolescence predict adverse socioeconomic and health outcomes in adulthood. This is an essential issue to investigate, as prevention of serious outcomes later in life is an important task for clinicians working with ADHD. Results from a study using a clinical adolescent ADHD sample found that low academic achievers, compared to high academic achievers, displayed more ADHD symptoms, although group differences were larger for parent-ratings (medium effect size; Cohen's $d = 0.60$) than self-ratings (small effect size; Cohen's $d = 0.26$) [8]. Another clinical study of young adults investigated how strongly parent- and self-reports of ADHD during interviews were associated with life events, including academic, occupational and criminal events, after accounting for reports from the other informant [9]. The study found that parent-reports of ADHD symptoms were significantly associated with all events, while self-reports were only significantly associated to employer-rated ADHD and work performance. The findings suggest that parent-reports of ADHD in young adults are more strongly associated to life outcomes and thus have higher concurrent validity than self-reports of ADHD. Similar results were found in a clinical sample of females with ADHD, where parent-rated ADHD symptoms were significantly associated with a higher number of poor outcomes than self-ratings [10]. A major limitation of these studies is that the majority of outcomes were rated subjectively, by the individuals, their parents or employers, which may have biased the results as associations may become inflated due to common method variance between predictor and outcome. Further, large-scale and longitudinal population-based studies that compare the predictive value of parent- and self-ratings of ADHD symptoms in adolescence are currently lacking.

Prospective studies have shown that ADHD in childhood predicts later adverse life outcomes [5, 11, 12], but less is known about the predictive value of ADHD in adolescence and whether it changes across development. To our knowledge, no study has compared the predictive associations between parent- and self-rated ADHD symptoms across adolescence and life outcomes in adulthood. If one of the two source informants would be superior in predicting serious life outcomes, it would suggest that the source informant provides a more accurate assessment of the individual's ADHD symptomatology and impairment, as ADHD diagnoses predict a range of adverse life outcomes [1–5]. Prospective studies have for example shown that individuals with ADHD are at increased risk of poor educational and occupational performance [1, 13], traffic injuries [3], substance and violence related crimes and convictions [5, 14] and disorders, such as substance use disorders (SUDs) and suicide attempt [2, 25]. Further, if the predictive strength of ADHD ratings varies across ages, it would be valuable to identify when in development parent- and self-ratings have more or less accurate prognostic values. This in turn could be used to inform clinicians about which informant at which stage in development is more or less valid as a predictor of risk for adverse life outcomes.

In this longitudinal, population-based study, we aimed to examine the predictive associations of parent- and self-ratings of ADHD symptoms in adolescence on assessments of adverse socioeconomic and health outcomes from Swedish national registries. We aimed to (1) compare how well parent- and self-ratings of ADHD symptoms assessed in early and late adolescence predict academic, occupational, social and psychiatric outcomes in young adulthood and (2) examine whether parent- and self-ratings of ADHD symptoms independently predict these outcomes over and above the other informant, to examine whether the source informants provide any unique information. We predicted that parent-ratings of ADHD symptoms would more strongly predict adverse life outcomes than self-ratings based on previous research suggesting that parent-report of ADHD in adolescence has greater construct and concurrent validity.

Methods

Sample

This study used data from the Twin Study of Child and Adolescent Development [15]. The target sample consisted of all 1480 twin pairs born in Sweden between May 1985 and December 1986. Data on life outcomes were derived through linkage of several nationwide population-based registers in Sweden, last updated in 2009. Individuals who had either died ($N = 12$; obtained from the Cause of Death Register) or emigrated ($N = 57$; according to the Migration Register) before or during year 2009, when registries were last updated, were excluded from analyses.

Individuals and one of their parents were assessed at two separate time points via mailed questionnaires; at age 13–14 years, 1063 (73%) parents and 2263 (78%) adolescents responded, and at age 16–17 years, 1067 (74%) parents and 2369 (82%) adolescents responded, with a majority of parent-rated information supplied by mothers. Informed consent was appropriately obtained and each wave of data collection was approved separately by

the ethics committee of Karolinska Institutet, Stockholm, Sweden.

Measures

ADHD symptoms

Parent-ratings consisted of 11 items from the Attention problem (AP) Scale of the Child Behavior Checklist (CBCL) and self-ratings consisted of nine items from the same AP Scale from the Youth Self-Report form (YSR) [16, 17]. The YSR consists of the same items as those in the CBCL except for 'nervous movements or twitching' and 'stares blankly'. The CBCL and YSR are standardized questionnaires used to rate children's behavioral and emotional problems exhibited in the past 6 months. The AP Scale, which assesses problems related both to inattention and hyperactivity-impulsivity, has been found to predict DSM (Diagnostic and Statistical Manual of Mental Disorders) diagnoses of ADHD [18, 19] and show good reliability, as well as convergent and discriminative validity [16, 17, 20]. Items were scored on a 3-point scale (0 = not true; 1 = sometimes true; and 2 = often true). The correlation coefficient (r) between parent- and self-rated symptoms was 0.36 ($p < 0.001$) at 13–14 years and 0.37 ($p < 0.001$) at 16–17 years of age, which is consistent with previous research [9, 21]. The correlation coefficient for parent-ratings over time was 0.63 ($p < 0.001$) and for self-ratings over time was 0.56 ($p < 0.001$).

Outcome information

Data on life outcomes were derived through linkage of nationwide population-based registers in Sweden; unique personal identification numbers enabled accurate linkage [21]. The National Patient Register (NPR) has coverage for psychiatric in-patient care and information on out-patient visits to specialist physicians since 2001, with diagnoses based on the International Classification of Diseases (ICD) [22]. The Prescribed Drug Register includes information on prescribed medical drugs since July 2005. The Migration Register supplies migration dates and the Cause of Death Register includes all mortality dates since 1958. The National Crime Register includes information about all criminal convictions in lower courts since 1973 [23]. The Longitudinal Integration Database for Health Insurance and Social Studies contains yearly assessments of a wide range of socio-demographic factors, including income, marital status, social welfare recipiency, and the highest achieved educational level for all individuals aged 15 years or older since 1990.

Education The academic variable was operationalized as not completing 2 or more years of higher (post-secondary) education, which was coded as a binary outcome (i.e., 1 = not completed, 0 = completed), and was obtained from the Education Register [24].

Occupation The occupational outcome was operationalized as receiving unemployment benefits, which was coded as a binary variable (i.e., 1 = received benefits, 0 = not received benefits), and was obtained from the Longitudinal Integration Database for Health Insurance and Social Studies. Unemployment was indexed by having received any benefits for being unemployed at least once for a period of at least 3 years during or after the age of 20 years (year 2006), which is the age at which you can claim unemployment benefits.

Criminality Criminality was identified through the National Crime Register. Convictions were obtained for substance-related crimes (i.e., making, transfer, possession, or use of illegal substances) and violent crimes (i.e., homicide, assault, threat or harassment, robbery, or arson). Criminality was indexed by any substance-related or violent criminal conviction during or after the age of 17 and 18 years (year 2003; after the last ADHD assessment was completed) and was coded as a binary variable (i.e., 1 = has been convicted, 0 = has not been convicted).

Unintentional injury Unintentional injuries were defined as any serious transport injuries, identified as emergency hospital visits due to transport-related trauma (codes V01–V99 in the International Classification of Diseases, Tenth Revision) via the NPR, which has previously been associated to ADHD in a large population-based study [3]. The outcome was indexed as any transport-related injury during or after the age of 17 and 18 years (year 2003) and was coded as a binary variable (1 = experienced unintentional injury, 0 = not experienced unintentional injury).

Psychiatric outcomes The psychiatric outcomes we studied were suicide attempt, SUDs and ADHD. We specifically chose to study suicide attempt and SUDs as we aimed to examine serious psychiatric outcomes, capturing both externalizing (SUD) and internalizing (suicide attempt) conditions that have previously been associated with ADHD [2, 25].

Suicide attempt was defined as any record of a suicide attempt from the NPR (ICD-8 and ICD-9 codes E950-E959, E980-E989; ICD-10 codes X60-X84, Y10-Y34) during or after the age of 18 years. Suicide attempt was coded as a binary variable (1 = suicide attempt, 0 = no suicide attempt).

SUD was indexed as a diagnosis of any SUD from the NPR (ICD-8 codes 303-304; ICD-9 codes 303-304, 305A, 305X; ICD-10 codes F10-F19) during or after 18 years. SUD was coded as a binary variable (1 = diagnosis of substance use disorder, 0 = no diagnosis of substance use disorder).

Individuals with a diagnosis of ADHD were identified from the NPR (ICD-9 code 314; ICD-10 code F90) by having at least 1 record of in-patient (between January 1, 1987, and December 31, 2009) or out-patient (from year 2001 onwards) care for ADHD. We also classified individuals treated with ADHD medication between 2005 and 2009 as patients with ADHD. These criteria have previously been validated as indicators of an ADHD diagnosis [26].

As only 22 (0.9%) individuals met criteria for ADHD, we did not include ADHD diagnosis as an outcome variable due to insufficient power. The prevalence of having been diagnosed with ADHD in our sample is much lower than in the general population (5.3%). This can be explained by the lack of data on out-patient diagnoses before year 2001 (participants were 15–16 years) and prescribed drugs before year 2005 (participants were 19–20 years). As ADHD is often first diagnosed in childhood, it is likely we have failed to identify individuals that only received a diagnosis in childhood.

Statistical analyses

We ran logistic regression models to examine how well parent- and self-ratings could predict life outcomes in young adulthood. We adjusted the standard errors for the clustered data structure (e.g., individuals being nested within twin pairs) using a cluster-robust sandwich estimator. The models were run separately for each informant source (parent- and self-ratings), age group (13–14 and 16–17) and life outcome. We also ran models where both informant-ratings were fitted as predictors in one model, to examine the unique predictive value of parent- and self-ratings after controlling for the other informant. Odds ratios (ORs) are used to quantify the strength of the associations and are presented along with 95% confidence intervals. Area under the receiver operating characteristic curve (AU-ROC) is used to quantify the discriminative accuracy of parent- and self-ratings of ADHD symptoms on the outcomes. We additionally investigated the discriminative accuracy of models including both parent- and self-ratings of ADHD symptoms.

We further dichotomized the ADHD symptom variables using cut-offs at the 90th centile and displayed the odds of experiencing life outcomes if individuals were over or under the 90th centile (Figs. 1, 2). We also ran sensitivity tests using the 95th centile to investigate whether the pattern of results were similar when we used a cut-off which corresponds to the estimated prevalence of ADHD (~5%).

Sensitivity analyses As there were differences in the amount of missing data for self- ($N = 722$ at time 1, $N = 594$ at time 2) and parent-ratings ($N = 828$ at time 1, $N = 853$ at time 2), we ran sensitivity analyses to examine whether differences in data missingness influenced any differences observed in the associations between self- and parent-rated ADHD symptoms and the outcomes. We re-ran the logistic regression models only including cases where neither self- nor parent-ratings were missing. To examine the potential effects of sex, we ran sensitivity analyses on males and females separately.

We additionally re-ran the analyses using parent-ratings of ADHD symptoms while excluding the two items that were absent in the self-rating scale, to examine whether differences in items between the two ratings scales influenced any differences observed in their associations with outcomes. All of the models were fitted in Stata 13 [27].

Results

See Table 1 for the frequency of adverse socioeconomic and health outcomes and the number of parent- and self-rated ADHD symptoms in early and late adolescence. Adolescents rated their levels of ADHD symptoms as more severe than parents at both 13–14 and 16–17 years.

Predictive value of parent- and self-rated ADHD symptoms at 13–14 and 16–17 years on life outcomes in early adulthood

13–14 years

Figure 1 depicts the odds of experiencing each life outcome for individuals that score over the 90th centile on the distribution of ADHD symptoms compared to under the 90th centile at 13–14 years. For parent-ratings, the odds of being in an accident, being criminal, not completing higher education, and having a SUD (OR = 1.80–2.96) were significantly higher for individuals in the top 10% compared to the lower 90% of ADHD symptom distribution. For self-ratings, however, only the odds of having a SUD (OR = 2.56) was significantly higher for individuals in the top 10% compared to the lower 90% of the distribution.

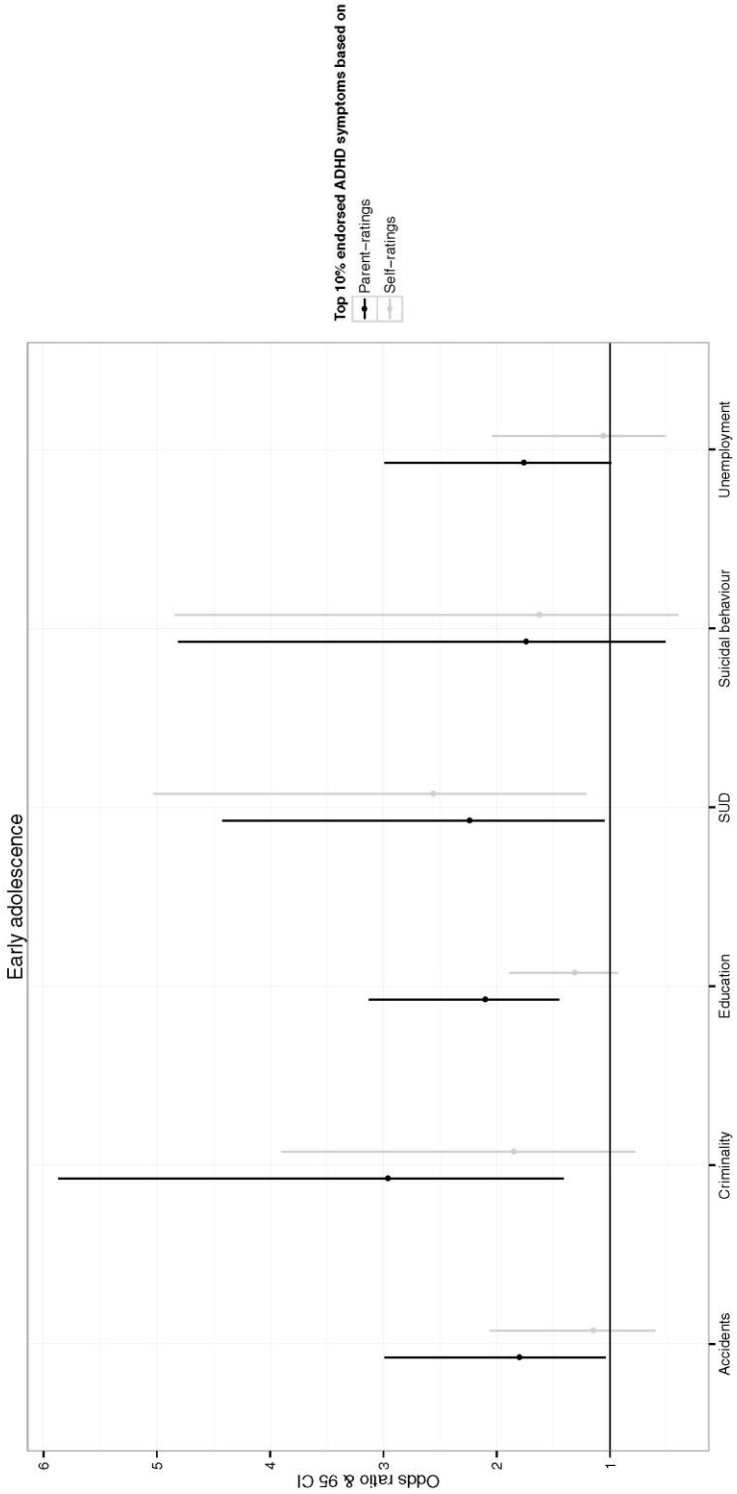

Fig. 1 Odds of experiencing each adverse socioeconomic and health outcome if individuals score >90th centile compared to <90th centile on ADHD symptoms rated by each informant in early adolescence. *SUD* substance use disorder

Table 1 Rates of adverse socioeconomic and health outcomes in young adulthood

	Women ($N = 1507$)	Men ($N = 1436$)	Total (%) ($N = 2944$)
Rates (%) of adverse socioeconomic outcomes			
No higher education	1099 (73%)	1163 (81%)	2262 (77%)
Unemployment	71 (5%)	61 (4%)	132 (4%)
Criminal conviction	17 (1%)	80 (6%)	97 (3%)
Rates (%) of adverse health outcomes			
Traffic-related injury	78 (5%)	79 (6%)	157 (5%)
Suicide attempt	24 (2%)	11 (1%)	35 (1%)
SUD diagnosis	38 (3%)	41 (3%)	79 (3%)
Mean (SD) ratings of ADHD symptoms at 13–14 years			
Self-rated	3.86 (2.69)	3.58 (2.71)	3.72 (2.70)
Parent-rated	1.16 (1.86)	1.58 (2.19)	1.36 (2.04)
Mean (SD) ratings of ADHD symptoms at 16–17 years			
Self-rated	4.22 (2.80)	3.38 (2.65)	3.82 (2.76)
Parent-rated	1.12 (1.80)	1.24 (1.96)	1.18 (1.88)

SUD substance use disorder, *SD* standard deviation

The logistic regression analyses showed that parent-rated ADHD symptoms at 13–14 years significantly predicted not completing higher education, unemployment, criminality, unintentional injuries and SUD (OR = 1.12–1.21; Table 2). The discriminative accuracy (AU-ROC) of parent-ratings on these adverse outcomes ranged between 0.58 and 0.65 (Table 3). Self-rated ADHD symptoms at 13–14 years also significantly predicted not completing higher education, criminality and SUD, with slightly lower point estimates (OR = 1.07–1.17) than parent-ratings, but did not predict unintentional injury or unemployment, or any other outcomes (Table 2). The discriminative accuracy (AU-ROC) of self-ratings on the significantly predicted adverse outcomes ranged between 0.55 and 0.62 (Table 3). The discriminative accuracy when both parent- and self-ratings were included in the logistic regression model ranged between 0.58 and 0.65. The AU-ROC values increased slightly when self-ratings were added in the model compared to when only parent-ratings were included for unemployment and SUDs, however, these changes were not significant as the confidence intervals were overlapping (Table 3).

16–17 years

Figure 2 depicts the odds of experiencing each life outcome for individuals that score over the 90th centile on the distribution of ADHD symptoms compared to under the 90th centile at 16–17 years. For parent-ratings, the odds of being criminal, not completing higher education and being unemployed (OR = 2.21–5.27) were significantly higher for individuals in the top 10% compared to the lower 90% of the ADHD symptom distribution. For self-report, however, only the odds of not completing higher education (OR = 1.81) was significantly higher for individuals in the top 10% of the distribution compared to the lower 90%.

Table 2 Predictive value of parent- and self-rated ADHD symptoms across adolescence on adverse socioeconomic and health outcomes in early adulthood

	Parent-ratings OR (95% CI)		Self-ratings OR (95% CI)	
	Crude	Adjusted for self-ratings	Crude	Adjusted for parent-ratings
13–14 years				
No graduate degree	1.21 (1.12, 1.31)**	1.18 (1.09, 1.28)**	1.07 (1.03, 1.11)**	1.03 (0.99, 1.08)
Unemployment	1.13 (1.05, 1.22)**	1.16 (1.07, 1.25)**	1.00 (0.92, 1.08)	0.97 (0.89, 1.05)
Criminality	1.21 (1.11, 1.32)**	1.20 (1.09, 1.32)**	1.11 (1.01, 1.23)*	1.02 (0.91, 1.15)
Injuries	1.12 (1.05, 1.20)**	1.11 (1.02, 1.19)**	1.07 (1.00, 1.14)	1.04 (0.96, 1.12)
Suicide attempts	1.13 (1.00, 1.28)	1.13 (0.97, 1.31)	1.09 (0.95, 1.26)	1.00 (0.85, 1.18)
Substance use disorders	1.15 (1.05, 1.26)**	1.10 (0.98, 1.22)	1.17 (1.06, 1.29)**	1.10 (0.98, 1.23)
16–17 years				
No graduate degree	1.49 (1.35, 1.63)**	1.44 (1.30, 1.60)**	1.15 (1.10, 1.20)**	1.06 (1.01, 1.12)*
Unemployment	1.16 (1.07, 1.25)**	1.16 (1.06, 1.27)**	1.03 (0.96, 1.10)	0.99 (0.92, 1.07)
Criminality	1.29 (1.17, 1.43)**	1.23 (1.06, 1.42)**	1.15 (1.06, 1.25)**	1.09 (0.95, 1.24)
Injuries	1.13 (1.04, 1.22)**	1.11 (1.02, 1.22)*	1.06 (1.00, 1.13)	1.01 (0.93, 1.09)
Suicide attempts	1.19 (1.03, 1.37)*	1.11 (0.93, 1.33)	1.12 (1.00, 1.25)*	1.10 (0.96, 1.26)
Substance use disorders	1.20 (1.07, 1.34)**	1.12 (0.96, 1.30)	1.14 (1.05, 1.25)**	1.13 (1.01, 1.27)*

** p value ≤ 0.01, * p value ≤ 0.05

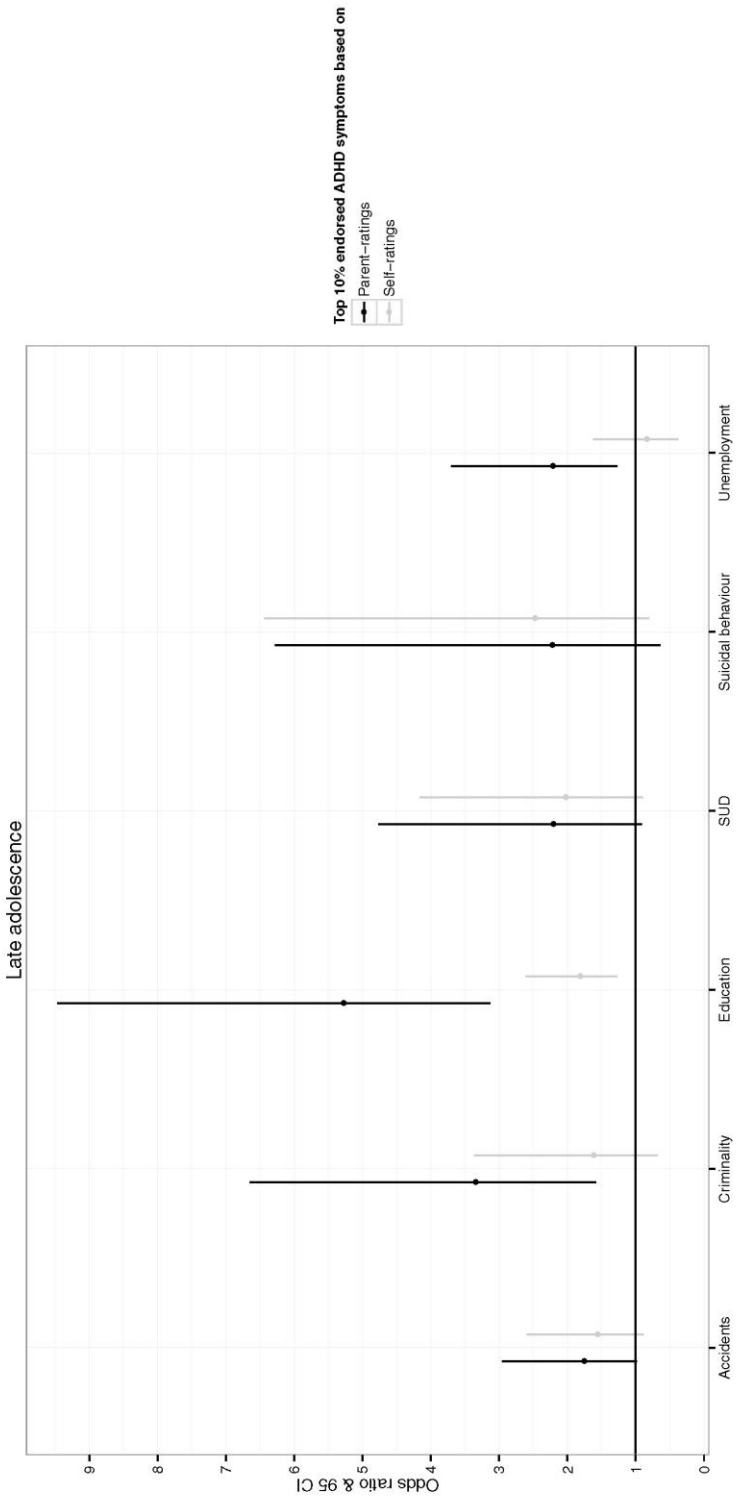

Fig. 2 Odds of experiencing each adverse socioeconomic and health outcome if individuals score >90th centile compared to <90th centile on ADHD symptoms rated by each informant in late adolescence. *SUD* substance use disorder

Table 3 Discriminatory accuracy of parent- and self-rated ADHD symptoms on adverse socioeconomic and health outcomes estimated by the area under the receiver operating characteristic curve (AU-ROC)

	Parent-ratings AU-ROC (95% CI)	Self-ratings AU-ROC (95% CI)	Parent- and self-ratings AU-ROC (95% CI)
13–14 years			
No graduate degree	0.59 (0.56, 0.61)	0.55 (0.52, 0.58)	0.59 (0.56, 0.62)
Unemployment	0.58 (0.52, 0.64)	0.50 (0.44, 0.56)	0.60 (0.54, 0.66)
Criminality	0.65 (0.56, 0.73)	0.59 (0.51, 0.68)	0.65 (0.57, 0.74)
Injuries	0.61 (0.56, 0.66)	0.56 (0.50, 0.61)	0.61 (0.55, 0.67)
Suicide attempts	0.58 (0.47, 0.69)	0.56 (0.44, 0.69)	0.58 (0.46, 0.71)
Substance use disorders	0.59 (0.51, 0.68)	0.62 (0.53, 0.70)	0.60 (0.52, 0.69)
16–17 years			
No graduate degree	0.62 (0.60, 0.64)	0.61 (0.58, 0.63)	0.64 (0.61, 0.66)
Unemployment	0.60 (0.54, 0.65)	0.52 (0.47, 0.58)	0.58 (0.51, 0.65)
Criminality	0.69 (0.61, 0.77)	0.63 (0.56, 0.71)	0.72 (0.64, 0.80)
Injuries	0.57 (0.51, 0.62)	0.55 (0.50, 0.61)	0.56 (0.50, 0.62)
Suicide attempts	0.62 (0.50, 0.73)	0.61 (0.51, 0.72)	0.64 (0.53, 0.75)
Substance use disorders	0.60 (0.50, 0.69)	0.62 (0.54, 0.71)	0.65 (0.56, 0.74)

The logistic regression analyses showed that parent-rated ADHD symptoms at 16–17 years significantly predicted all outcomes in early adulthood (OR = 1.13–1.49; Table 2). The discriminative accuracy (AU-ROC) of parent-ratings on the outcomes ranged between 0.57 and 0.69 (Table 3). Self-rated ADHD symptoms significantly predicted all outcomes except for unintentional injuries and unemployment (OR = 1.035–1.15; Table 2). The discriminative accuracy (AU-ROC) of self-ratings on these adverse outcomes ranged between 0.52 and 0.63. The discriminative accuracy when both parent- and self-ratings were included in the logistic regression model ranged between 0.56 and 0.72. The AU-ROC values increased slightly when self-ratings were added in the model compared to when only parent-ratings were included for all outcomes except for unemployment and accidents, however, these changes were not significant as the confidence intervals were overlapping.

Unique predictive value of parent- and self-rated ADHD symptoms at 13–14 and 16–17 years on life outcomes in early adulthood, over and above the other informant

13–14 years

Parent-rated ADHD symptoms at 13–14 years of age significantly predicted not completing higher education, unemployment, criminality and unintentional injuries when controlling for self-ratings (OR = 1.11–1.20). Self-rated ADHD symptoms did not significantly predict any outcomes in early adulthood when controlling for parent-ratings (Table 2).

16–17 years

Parent-rated ADHD symptoms at 16–17 years significantly predicted not completing higher education, unemployment, criminality and injuries (OR = 1.11–1.44), when controlling for self-ratings. Self-ratings of ADHD symptoms at 16–17 years significantly predicted not completing higher education and SUD (OR = 1.06–1.13) over and above parent-ratings (Table 2).

Sensitivity analyses

The pattern of results did not change when we excluded cases that had missing values of either parent- or self-ratings (Table S1) or when analyses were run on males and females separately (Table S2 and S3). However, higher self-ratings of ADHD symptoms in late adolescence uniquely predicted less unemployment while controlling for parent-ratings only in males. Further, both parent- and self-rated ADHD symptoms showed slightly higher predictive values on life outcomes in males than in females.

Parent-ratings showed similar associations with the outcomes with and without the two additional ADHD rating scale items, suggesting that differences between parent- and self-rated symptoms in their associations with life outcomes is not explained by differences in rating scale items (Table S4). There was, however, one exception; parent-ratings no longer significantly predicted unemployment over and above self-ratings when parent- and self-rating scales included the same items.

We ran additional sensitivity analyses where we dichotomized the ADHD symptom variables using cut-offs at the 95th centile to explore the odds of experiencing

life events for individuals over or under the 95th centile. The overall pattern of results remained the same when we used the 5% cut-off as when the 10% cut-off was used (Table S5).

Discussion

In this longitudinal, population-based study, we found that both parent- and self-ratings of ADHD symptoms rated in adolescence predicted several important adverse life outcomes in early adulthood. In general, the associations between ADHD symptoms and outcomes were stronger in late compared to early adolescence, and parent-ratings of ADHD symptoms predicted several outcomes over and above self-ratings in both early and late adolescence. The findings suggest that clinicians can rely on both informant sources in adolescence for predicting risk of future adverse socioeconomic and health outcomes, although some caution should be placed on self-ratings of ADHD in early adolescence.

Past research has repeatedly shown that ADHD symptoms rated by parents in childhood are associated with adverse life outcomes, and our current results extend these findings to show that both parent- and self-rated symptoms in adolescence were significantly associated with adverse outcomes. For clinicians, these findings suggest that both informant sources in adolescence may provide valuable information for risk of serious outcomes in adulthood. However, we found that the discriminatory accuracy of both parent- and self-rated ADHD symptoms were low, suggesting that neither can be used to accurately discriminate between adolescents who will experience adverse outcomes from those who will not. Although the response rate of our twin study is high, non-responders are more likely to be male and have higher rates of ADHD symptoms in childhood [28, 29]. Given that previous research indicates that associations between ADHD symptoms and behavioral problems increase along with increasing levels of symptom severity, this may suggest that our observed associations between ADHD symptoms and adverse socioeconomic and health outcomes are somewhat underestimated.

Parent-ratings of ADHD symptoms rated in early and late adolescence were generally more strongly associated with the life outcomes compared to self-ratings, although it should be noted that the confidence intervals of the ORs overlapped for most outcomes, suggesting that the difference between parent- and self-ratings in their predictive strength did not significantly differ. Further, parent-ratings predicted several outcomes over and above self-ratings, and the discriminative accuracy did not significantly improve when self-ratings were added to the models compared to when only parent-ratings were used. Our findings suggest that despite parent- and self-ratings of ADHD symptoms only showing modest correlations (0.36–0.37), self-ratings do not have added value beyond parent-ratings for most life outcomes. While multi-informant approaches (e.g., combining informant source ratings) are commonly used based on the belief that each informant provides unique and valuable information, our results suggests that self-ratings are not valuable once parent-ratings have been taken into account in predicting most outcomes, except for SUDs. One possible explanation for the finding that self-ratings significantly predicted SUDs beyond parent-ratings may be that individuals more likely base their ratings of ADHD symptoms on aspects of behavior related to substance use, which parents may not have as much insight into. Our findings are consistent with other lines of research suggesting that parent-ratings have higher concurrent and construct validity than self-ratings in adolescence [30–32] and young adulthood [10]. For example, one study found higher agreement between parent-ratings of ADHD and clinicians (during interviews with parents) than between self-ratings of ADHD and clinicians (during interviews with children and adolescents) [30]. Another study found that parent-ratings of ADHD symptoms were more predictive of ADHD diagnostic group than self-ratings [31]. Parent-ratings of ADHD have also been found to be more strongly associated with underlying objective (cognitive, neurophysiological and movement) indices of ADHD symptomology than self-ratings [32]. Thus, even though our findings suggest that self-ratings provide some prognostic information, the data indicate that obtaining parent-ratings of ADHD symptoms should be the priority in child and adolescent clinical and research settings.

Both parent- and self-rated ADHD symptoms showed an increase from early to late adolescence in the number of statistically significant associations and also in the effect sizes of the associations with the life outcomes. This overall increase in predictive value is not likely explained by a decrease in endorsed ADHD symptoms with age as parent-rated, but not self-rated, symptoms decreased only slightly (from 1.38 to 1.18). Instead, the findings may reflect the shorter time interval in the predictions with increasing age, or that both parents and adolescents become more accurate in their descriptions of the adolescent's ADHD symptomatology with age, although this second explanation is unlikely. Future work is needed to extend our findings and examine the predictive validity of parent- and self-rated ADHD in young adulthood. This would be informative in order to explore whether the predictive value of self-ratings increases at a specific point in development from adolescence to adulthood. This could be of great value for both clinicians and researchers when

having to decide at which age self-report should be used as the main reporting source of ADHD symptoms.

Sensitivity analyses revealed that differences in results between parent- and self-ratings of ADHD were overall not influenced by (1) differences in missing values or (2) differences in items included in the two rating scales. When we re-ran analyses for sex separately, we found that the pattern of results remained the same, although both parent- and self-rated ADHD symptoms in males showed slightly stronger associations with life outcomes than in females. The stronger associations might reflect that boys tend to display more externalizing features of ADHD than girls [33, 34], which may be more easily captured by rating scales.

It should be acknowledged that this study used a population-based sample, and therefore findings may not generalize to individuals with clinically diagnosed ADHD. Even though behavioral, clinical and etiological research converge in suggesting that ADHD symptoms are the extreme of a normal continuum of behavior in the general population [35, 36], it would be informative to examine the predictive validity of parent- and self-ratings in a clinical sample, especially as individuals in this study rated their levels of ADHD symptoms as more severe than their parents, which is in line with population studies [37] but inconsistent with clinical studies that tend to report higher levels of parent-rated symptoms [31, 32]. Further, the predictive validity of ratings that we have studied may also reflect concurrent validity, as for some outcomes the time period for which the outcomes were indexed in the registers started one year after the 16/17-years assessment wave, and therefore might already have been present during the assessment. Another possible limitation is that the predictive value of ADHD symptoms on life outcomes should be interpreted with caution due to the modest effect sizes for the majority of associations. Further, as the AU-ROC values were low, we conclude that neither parent- nor self-ratings of ADHD symptoms could accurately discriminate between individuals who experienced adverse outcomes to those who did not.

Conclusion

In conclusion, we found that both parent- and self-ratings of ADHD symptoms in adolescence were significantly associated with adverse socioeconomic and health outcomes in early adulthood. Parent-ratings of ADHD from early to late adolescence were better predictors of serious outcomes, although self-ratings in late adolescence significantly predicted not having a higher educational degree and SUD over and above parent-ratings. Our findings suggest that both informant-ratings of ADHD in adolescence provide valuable prognostic information on risk of future adverse life outcomes. However, clinicians should prioritize parent-ratings over self-rating, especially in younger adolescents.

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Compliance with ethical standards

Conflict of interest H. Larsson has served as a speaker for Eli-Lilly and Shire and has received a research grant from Shire; all outside the submitted work. E. Du Rietz, R. Kuja-Halkola, I. Brikell, A. Jangmo, A. Sariaslan, P. Lichtenstein and J. Kuntsi report no conflicts of interest.

Ethical standards Each wave of data collection was approved by the appropriate ethics committee, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants have their informed consent prior to their inclusion in the study.

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CHAPTER 4 – Association of polygenic risk for attention-deficit/hyperactivity disorder with co-occurring traits and disorders

Archival Report

Biological Psychiatry: CNNI

Association of Polygenic Risk for Attention-Deficit/Hyperactivity Disorder With Co-occurring Traits and Disorders

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ABSTRACT

BACKGROUND: A recent large-scale mega genome-wide association study identified, for the first time, genetic variants at 12 loci significantly associated with attention-deficit/hyperactivity disorder (ADHD). In this study we use a powerful polygenic approach, with polygenic scores derived from the genome-wide association study, to investigate the etiological overlap between ADHD and frequently co-occurring traits and disorders.

METHODS: Polygenic risk scores for ADHD derived from the mega genome-wide association study (20,183 cases and 35,191 control subjects) were computed in a large-scale adult population sample (N = 135,726) recruited by the UK Biobank. Regression analyses were conducted to investigate whether polygenic risk for ADHD is associated with related traits and disorders in this population sample. The effects of sex were investigated via inclusion of an interaction term in the models.

RESULTS: Polygenic risk for ADHD significantly and positively predicted body mass index (R^2 = .45%; $p = 5 \times 10^{-129}$), neuroticism (R^2 = .09%; $p = 2 \times 10^{-24}$), depression (R^2 = .11%; $p = 2 \times 10^{-13}$), anxiety (R^2 = .06%; $p = 3 \times 10^{-4}$), risk taking (R^2 = .12%; $p = 9 \times 10^{-25}$), alcohol intake (R^2 = .09%; $p = 8 \times 10^{-29}$), smoking (R^2 = .33%; $p = 4 \times 10^{-21}$), alcohol dependency (R^2 = .21%; $p = 5 \times 10^{-6}$), and negatively predicted verbal-numerical reasoning (R^2 = .38%; $p = 5 \times 10^{-36}$). Polygenic risk scores did not significantly predict schizophrenia or bipolar disorder, although this may be because of the small number of diagnostic cases. We found no interaction effects between polygenic risk for ADHD and sex on any phenotypes.

CONCLUSIONS: Our findings suggest that common genetic variation underlying risk for clinically diagnosed ADHD also contributes to higher body mass index, neuroticism, anxiety and depressive disorders, alcohol and nicotine use, risk taking, and lower general cognitive ability in the general population. These findings suggest that the co-occurrence of several traits with ADHD is partly explained by the same common genetic variants.

Keywords: ADHD, Comorbidity, Co-occurring disorders, Genetics, Pleiotropy, Polygenic risk

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A recent mega genome-wide association study (GWAS) was the first to identify 12 loci significantly associated with attention-deficit/hyperactivity disorder (ADHD) (1). The statistical power of this GWAS allows the investigation of aspects of the genetic etiology of ADHD and its co-occurring features through polygenic approaches. Typically in polygenic risk analyses, composite scores, known as polygenic risk scores (PRSs), are created for individuals based on the sum of their risk alleles across the genome, weighted by GWAS-derived effect sizes. These PRSs optimize the genetic signal underlying complex traits and disorders and have been widely used to investigate shared genetic etiology between phenotypes (2–4).

Previous GWAS and candidate studies failed to identify rare and common genetic variants underlying ADHD that explain more than a small fraction of its heritability (5–7), despite the high heritability of ADHD estimated at 0.76 from twin studies (8) and estimated at 0.22 to 0.32 based on single nucleotide polymorphisms (SNPs) (1,9). The difficulty in identifying genetic variants has likely been because of low statistical power and the polygenic nature of ADHD, i.e., that risk is a consequence of many small genetic effects. This has been supported by recent polygenic studies that show that significant associations emerge when a high number of genetic variants are considered en masse (1,10).

ADHD has a prevalence rate of around 5.3% in childhood and 2.5% to 2.9% in adulthood (11–13). While the diagnosis of ADHD is based on inattentive and hyperactive-impulsive symptoms, affected individuals often also experience other adverse conditions. Individuals with ADHD are more likely than the general population to present with higher body mass index (BMI) (14,15), neurotic (16) and risk-taking (17–19) behavior, lower IQ scores, and conditions such as bipolar disorder (BD), depression, anxiety (20–24), schizophrenia (24,25), and substance abuse (20,21,23,26,27).

SEE COMMENTARY ON PAGE 577

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Family and twin studies suggest that several of these associations between ADHD and co-occurring traits and disorders are moderately to substantially explained by genetic influences (24,25,28–34). Until recently, the genetic overlap between ADHD and associated traits and disorders had not been studied using genome-wide approaches; however, limited recent and yet unpublished studies using linkage disequilibrium score regression (LDSR) report significant genetic correlations between ADHD and BMI (r_g = 0.21–0.26), educational and cognitive measures (r_g = −0.25 to 0.54), depression (r_g = 0.48), BD (r_g = 0.25), schizophrenia (r_g = 0.22), and smoking (r_g = 0.38–0.48), but not neuroticism and obsessive-compulsive disorder (1,35). No genome-wide studies have yet investigated the genetic association between ADHD and risk taking, or alcohol and drug use.

While associations between ADHD and co-occurring impairments are well documented, our knowledge of the shared etiological influences underlying these co-occurrences is still limited with regard to the magnitude and type of genetic variants implicated in the genetic associations. The advantage of using a polygenic approach to study the genetic associations between phenotypes is that 1) we use molecular genetic data that do not rely on assumptions of relatedness, as in twin studies; 2) the design captures the polygenic nature of complex traits and disorders; and this design in turn 3) increases power to detect significant effects in studies compared with those considering only the most associated variants or candidate genes. In contrast to LDSR, the polygenic scoring method uses individual-level SNP, resulting in greater statistical power data and allowing for direct testing of interaction effects.

In this study, we use a powerful polygenic approach exploiting PRSs derived from the recently published mega GWAS on ADHD to test whether genetic variants that contribute to ADHD also influence frequently co-occurring traits and disorders in a large-scale adult population sample. A greater understanding of why ADHD often co-occurs with other impairing conditions may in turn improve preventative strategies and treatment for affected individuals. We further investigate whether the genetic overlap between ADHD and co-occurring features varies as a function of sex. Although a recent study suggested a near complete overlap of common genetic variants associated with ADHD between males and females (36), there may be sex differences in the genetic overlap between ADHD and comorbid features.

METHODS AND MATERIALS

Discovery Sample

We used the recently published mega GWAS on ADHD as the discovery dataset (1). Summary results were downloaded from the PGC website (https://www.med.unc.edu/pgc/results-and-downloads). This GWAS contains data from 55,374 children and adults (20,183 ADHD cases and 35,191 control subjects), and 8,047,421 SNPs. Twelve independent loci were significantly associated with ADHD, and polygenic risk calculated from the GWAS explained on average up to 5.5% variance in ADHD case-control status, when using five different sets of discovery and independent target samples. The SNP-based heritability was calculated as 0.22 (1).

Target Sample

Participants. We used baseline data from the UK Biobank Study (http://www.ukbiobank.ac.uk) (41). A total of 502,655 community-dwelling participants between 37 and 73 years of age were recruited between 2006 and 2010 through the United Kingdom National Health Service patient registers (response rate = 5.47%) and underwent extensive cognitive and physical assessments. We analyzed data on 135,726 individuals (71,874 females) between 40 and 73 years of age (mean ± standard deviation [SD], 56.79 ± 7.96 years) who had available genotyping data after quality control (detailed below). UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/0382).

Genotyping and Quality Control. A total of 152,729 blood samples were genotyped using either the UK Biobank Lung Exome Variant Evaluation array (N = 49,979) or the UK Biobank axiom array (N = 102,750). Details on genotyping, quality control, and imputation procedures can be found on the UK Biobank website (http://www.ukbiobank.ac.uk/scientists-3/genetic-data/) and Sudlow *et al.* (37). We further excluded SNPs based on minor allele frequency (<0.01), Hardy-Weinberg equilibrium ($p < 10^{-8}$), and missingness (>0.02), and removed participants based on missingness (>0.01), relatedness (>0.088 [$r\sim$ = .25]), gender mismatch, and non-Caucasian ancestry. Table 1 shows the sample sizes after quality control for each phenotype. The resulting dataset had 512,536 SNPs and 135,726 samples available for analysis.

Phenotypes: BMI. BMI, which is constructed from weight and height (kg/cm^2), was measured during the initial assessment. BMI values were excluded if data on either height or weight were missing.

Table 1. Rates of Diagnoses and Mean Scores on Target Phenotypes

Target Phenotypes	Value	Total, *n*
Continuous Phenotypes, Mean ± SD		
Verbal-numerical reasoning	6.11 ± 2.11	43,637
Neuroticism	4.11 ± 3.27	110,213
Alcohol intake frequency	2.89 ± 1.50	135,586
Body mass index, kg/cm^2	27.52 ± 4.84	135,348
Binary Phenotypes, *n* (%)		
Anxiety disorder	2575 (2.14)	120,362
Depressive disorder	8818 (6.96)	126,605
Bipolar disorder	2232 (1.86)	120,019
Schizophrenia	288 (0.24)	118,075
Alcohol dependency	988 (0.83)	118,775
Risk-taking	39,245 (29.00)	135,348
Tobacco use	2911 (2.15)	135,348

Verbal-numerical reasoning score was assessed as the number of correctly answered multiple choice questions (range, 0–13). Neuroticism was assessed as the number of neurotic traits present (range, 0–12). Alcohol intake frequency was scored as follows: 5 = daily or almost daily; 4 = 3 or 4 times a week; 3 = 1 or 2 times a week; 2 = 1 to 2 times a month; and 1 = special occasions only.

Phenotypes: General Cognitive Ability. Participants completed a verbal-numerical reasoning test, consisting of 13 multiple choice questions (6 verbal/7 numerical) answered within a 2-minute time period (Supplemental Table S1). The test has shown a satisfactory level of test–retest reliability (r = .65) and a high genetic correlation with a general factor of cognitive ability (r_g = .81, $p = 6.2 \times 10^{-18}$) (38,39).

Phenotypes: Internalizing Traits and Psychiatric Disorders. Neuroticism was measured using 12 items (Supplemental Table S2) from the Eysenck Personality Inventory Neuroticism Scale–Revised (40). The score of each individual corresponds to the number of neurotic traits present, each coded as a binary variable (1 = yes, 0 = no).

Primary (the most resource-intensive condition) or secondary ICD-10 diagnoses (accessed through hospital records) and self-report measures (reports of having experienced a disorder during an interview with a nurse) were used to identify individuals who had experienced instances of anxiety and depressive disorders, BD, and schizophrenia (ICD-10 codes can be found in Supplemental Table S3). Individuals were indexed as having experienced a psychiatric disorder if they met criteria either through self-report or an ICD-10 diagnosis (any ICD subtype as seen in Supplemental Table S3).

Phenotypes: Substance Use and Risk-Taking. Alcohol intake frequency was measured by asking participants "About how often do you drink alcohol?" and was coded on a 5-point scale (Supplemental Table S4). Primary or secondary ICD-10 diagnoses (accessed through hospital records) and self-report measures (reports of having experienced a disorder during an interview with a nurse) were used to identify individuals that had ever experienced alcohol dependency or a mental/behavioral disorder owing to alcohol use (Supplemental Table S3). Information on smoking (ICD-10 code Z72.0) was accessed through hospital records. Risk-taking was measured by asking participants "Would you describe yourself as someone who takes risks?" and was coded as a binary variable (1 = yes, 0 = no).

The control group used for comparisons with the diagnostic groups consisted of individuals that did not have any ICD-10 or self-reported diagnosis of alcohol dependency, anxiety disorder, depressive disorder, BD, or schizophrenia and did not take lithium, antidepressants, or antipsychotics.

We did not investigate participants with ADHD because only 7 individuals had an ICD-10 diagnosis (secondary) for ADHD or were taking stimulant medications (methylphenidate or Ritalin) in our genotyped sample. There were also few participants ($n < 25$) diagnosed with oppositional defiant disorder, conduct disorder, or autism spectrum disorder. The low prevalence rate of ADHD and these other disorders in the UK Biobank is likely related to the older age of the sample (40–73 years of age), as they are most often diagnosed in childhood but were not as commonly recognized when participants were school-aged children.

Phenotypes: Control Traits. We also investigated eight "control" phenotypes that we did not expect to be significantly associated with PRS ADHD, in order to confirm that any reported significant results were not caused by the inflation of type I errors. These control traits were height, age, year of initial assessment, menstruation during initial assessment, number of self-reported cancers, hand grip strength, visual acuity, and sex of baby (Supplemental Table S5).

PRS Analyses

PRSs were computed for each UK Biobank participant using PRSice software (http://www.prsice.info/) (41), with the mega GWAS summary statistics as the discovery dataset. PRSice computes scores by calculating the sum of trait-associated alleles, weighted by the odds ratio generated from a GWAS in an independent sample. An $r^2 \geq .1$ (250-kb window) was used for clumping to remove SNPs in linkage disequilibrium. Logistic and linear regression models were used to estimate associations between PRSs and phenotypes in the UK Biobank. PRSs were calculated at a large number of p value thresholds for SNP inclusion ("high resolution scoring") (41) to provide the most predictive PRS. p Value thresholds were between $p_T = 0$ and $p_T = 0.5$ at increments of .001. Results are presented where the most predictive PRS is identified for each phenotype. We set a conservative significance threshold of $p < 2.1 \times 10^{-4}$ for the main analyses on traits of interest and "control" traits, based on testing the most predictive PRS across 19 phenotypes (see Supplemental Methods).

We controlled for population stratification by conducting analyses with imputed markers and 15 principal components as covariates. We included birthplace, age, and sex as covariates in all analyses, and also batch, in order to control for any genetic differences associated with the batches that samples were analyses in or the genotyping platforms. The R^2 values we report are adjusted from a baseline model including the covariates. In addition, we ran secondary analyses where we explored the effect of sex by including PRS by sex interaction effects. For these analyses, we set a stringent significance threshold of $p < 4.5 \times 10^{-4}$ (see Supplemental Methods). In the prediction model for height, we added BMI as a covariate because of the significant phenotypic association between BMI and height ($r = -.0145$, $p = 1.07 \times 10^{-24}$).

RESULTS

Table 1 summarizes the number of individuals included in analyses for each target phenotype and presents mean values and standard deviations for the continuous phenotypes and the number of "cases" for the binary phenotypes.

Body Mass Index

PRS for ADHD significantly ($p = 4.5 \times 10^{-129}$) predicted BMI (R^2 = .45%, p_T = .44) (Figure 1), and the quantile plot demonstrates the positive nature of this relationship as BMI increases with greater polygenic load for ADHD (Figure 2). Mean BMI was significantly higher in males (mean ± SD, 27.95 ± 4.31) than in females (27.14 ± 5.23).

General Cognitive Ability

PRS for ADHD significantly ($p = 4.5 \times 10^{-36}$) predicted verbal-numerical reasoning scores (R^2 = .38%, p_T = .42) (Figure 1), and the quantile plot shows that verbal-numerical reasoning scores decreased with increasing polygenic load for ADHD

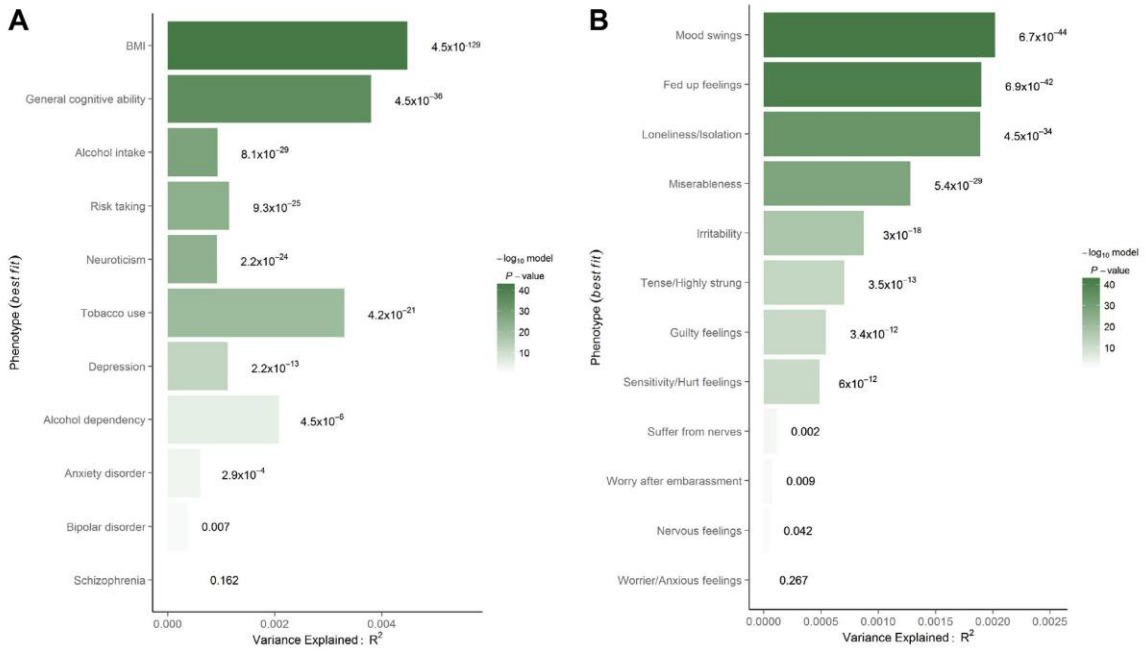

Figure 1. Association between polygenic risk scores for attention-deficit/hyperactivity disorder and **(A)** target phenotypes and **(B)** items on the neuroticism scale. Values displayed next to each bar represent the p value for significance for the most predictive models. The significance threshold was set to $p < 2.1 \times 10^{-4}$. BMI, body mass index.

(Figure 2). Verbal-numerical reasoning test scores were significantly higher in males (6.22 ± 2.18) than in females (6.01 ± 2.05).

Internalizing Traits and Psychiatric Disorders

PRS for ADHD significantly ($p = 2.2 \times 10^{-24}$) predicted neuroticism (R^2 = .09%, p_T = .14) and the quantile plot demonstrates that neuroticism scores increase with higher polygenic load for ADHD (Figure 2). Females showed significantly higher neuroticism levels (4.60 ± 3.26) than males (3.60 ± 3.20). We further investigated the separate 12 neuroticism items (Figure 1). PRS for ADHD significantly and positively predicted mood swings (R^2 = .002%), fed-up feelings (R^2 = .20%), feelings of loneliness and isolation (R^2 = .19%), miserableness (R^2 = .13%), irritability (R^2 = .09%), being tense/highly strung (R^2 = .07%), guilty feelings (R^2 = .05%), and having easily hurt feelings (R^2 = .05%). The PRS did not predict suffering from nerves, often worrying after embarrassment, or being a nervous person or a worrier.

PRS for ADHD also significantly ($p = 2.2 \times 10^{-13}$) predicted depressive disorder (R^2 = .11%, p_T = .03) and suggestively ($p = 2.8 \times 10^{-4}$) predicted anxiety (R^2 = .06%, p_T = .12) but not BD or schizophrenia (Figure 1). Quantile plots (Figure 2) show that the significant associations were positive. A significantly higher proportion of females than males presented with anxiety (2.6% vs. 1.6%), depression (8.5% vs. 5.2%), and BD (2.3% vs. 1.4%), but the opposite trend was observed for schizophrenia (0.2% vs. 0.3%).

Substance Use and Risk-Taking

PRS for ADHD significantly ($p < 2.1 \times 10^{-4}$) predicted risk-taking (R^2 = .12%, p_T = .29), alcohol intake frequency (R^2 = .09%, p_T = .23) and dependency (R^2 = .21%, p_T = .18), and smoking (R^2 = .33%, p_T = .49). Quantile plots suggest that all of these relationships were positive in nature (Figure 2). A significantly higher proportion of males than females were risk-takers (36.3% vs. 22.3%), alcohol dependent (1.2% vs. 0.4%), and smokers (2.5% vs. 1.8%). Females showed significantly higher alcohol intake frequency (3.14 ± 1.53) than males (2.60 ± 1.42).

We found no significant PRS by sex interaction effects for any of the target phenotypes (Table 2).

Control Phenotypes

PRS for ADHD significantly ($p < 2.1 \times 10^{-4}$) and negatively predicted height (R^2 = .03%, p_T = .08) and age (R^2 = .03%, p_T = .18), but not any of the remaining six control phenotypes (Table 3). After controlling for educational achievement (detailed in Supplemental Table S6), which has been found to be genetically associated with height (42), the significant association between PRS for ADHD and height was no longer significant (R^2 = .005%, p = .0001); however, the association between PRS and age remained and was significant in both males (R^2 = .021%, $p = 3 \times 10^{-5}$) and females (R^2 = .029%, $p = 8 \times 10^{-6}$). When we reran all the main analyses controlling for educational achievement and BMI, which were the two additional covariates in the

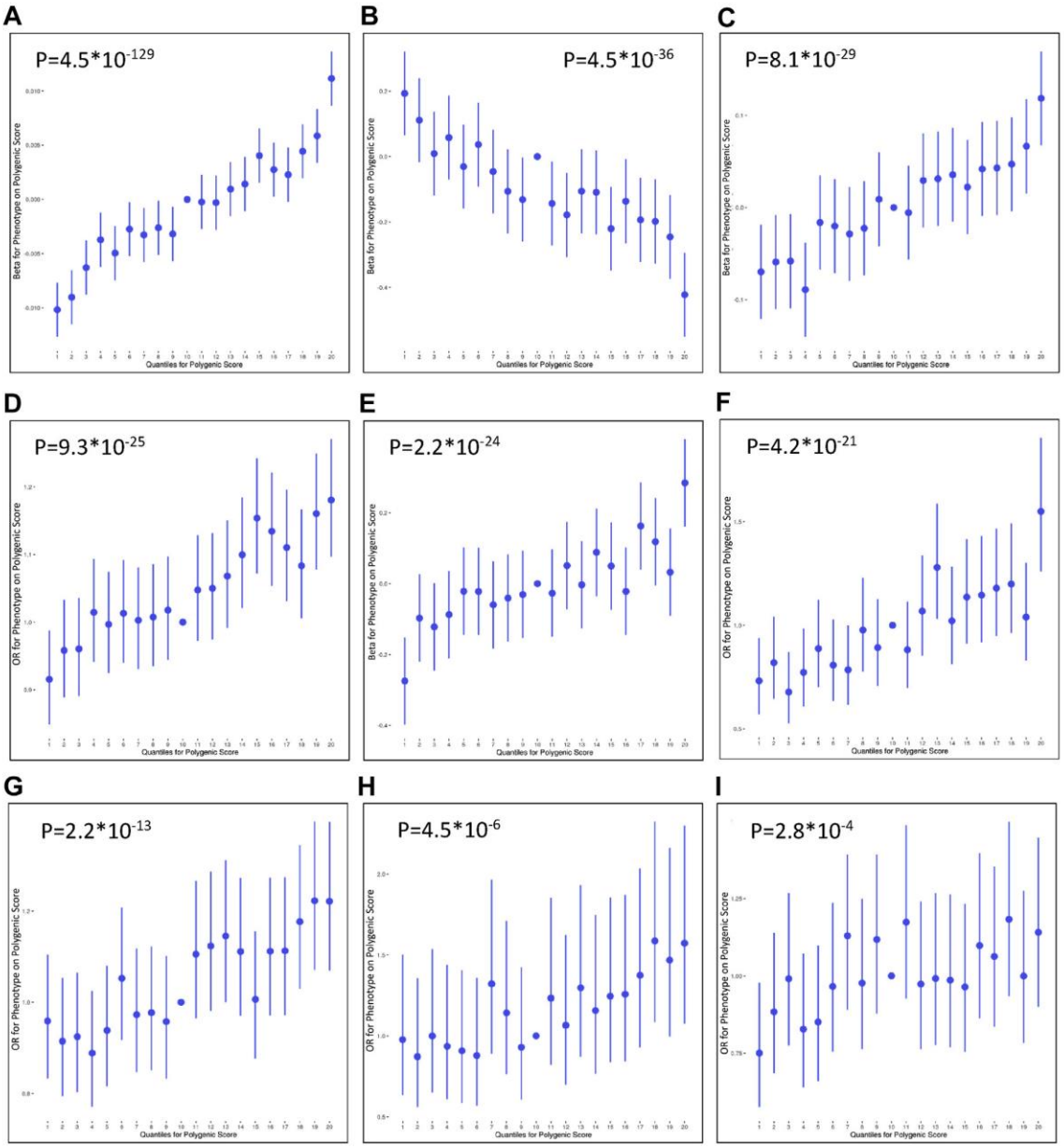

Figure 2. Quantiles of polygenic risk scores plotted against effects on phenotypes. **(A)** Body mass index; **(B)** verbal-numerical reasoning; **(C)** alcohol intake; **(D)** risk-taking; **(E)** neuroticism; **(F)** tobacco use; **(G)** depression; **(H)** alcohol dependency; and **(I)** anxiety disorder. A regression is performed with phenotype as outcome and each 5% quantile separately, whereby the effect size of each quantile is compared to the central quantile as reference, such that each polygenic score in the quantile in question is coded 1 and each polygenic score in the reference quantile is coded 0. In each regression, the covariates used in the main analyses are included. OR, odds ratio.

PRS–height model, the overall pattern of results remained the same, although effect sizes decreased for most traits (Supplemental Table S7).

Table 3 and Supplemental Figures S1 to S11 provide more detailed information and plots for the PRS prediction models.

Table 2. Polygenic Risk Score by Sex Interaction and Main Effects of Sex on Target Phenotypes

Target Phenotype	$PRS_{M\beta}$	$PRS_{F\beta}$	$p_{interaction}$	*t/z* Score	Sex_{β}	p_{sex}	*t/z* Score
Body Mass Index	0.07	0.07	.03	−2.23	0.10	1.55×10^{-725}	35.36
Verbal-Numerical Reasoning	−0.05	−0.07	.12	1.55	0.05	4.82×10^{-25}	10.34
Alcohol Intake	0.03	0.04	.11	−1.62	−0.18	$<2 \times 10^{-285}$	−66.46
Risk-Taking	0.15	0.14	.26	1.13	0.81	$<2 \times 10^{-285}$	57.70
Neuroticism	0.03	0.03	.52	−0.64	−0.15	$<2 \times 10^{-285}$	−49.19
Tobacco Use	1.10	1.33	.57	−0.56	1.02	5.79×10^{-14}	7.51
Depressive Disorders	0.45	0.27	.36	0.91	−1.07	2.55×10^{-116}	−22.93
Alcohol Dependency	1.28	2.93	.36	−0.92	5.45	1.79×10^{-39}	13.15
Anxiety Disorders	0.37	0.57	.37	−0.89	−1.62	1.69×10^{-28}	−11.07
Bipolar Disorder	0.21	0.53	.29	−1.06	−1.79	1.73×10^{-26}	−10.65
Schizophrenia	2.56	0.40	.29	1.06	4.35	.00071	3.39

Significance threshold set at $p < 4.5 \times 10^{-4}$.
$PRS_{M/F}$, prediction of polygenic risk score on target phenotype for males and females.

DISCUSSION

Using PRSs derived from the recently published mega GWAS (1), we found that polygenic risk for clinically diagnosed ADHD predicts higher BMI, neuroticism, risk-taking, tobacco and alcohol use, and anxiety and depressive disorders, and lower general cognitive ability in an adult population sample. These are the first reports of significant genetic associations between ADHD and neuroticism traits, risk-taking, and alcohol use based on genome-wide data. The remaining associations are consistent with a relatively limited literature of studies demonstrating pleiotropy of the genetic variants underlying ADHD. No sex-specific effects were observed in relation to the association between PRS for ADHD and co-occurring features.

Table 3. Prediction of Polygenic Risk Score for Attention-Deficit/Hyperactivity Disorder on Target and Control Phenotypes

Target or Control Phenotype	*p*	p_T	R^2 (%)	SNPs, *n*
Body Mass Index	4.5×10^{-129}	.440	.448	69,995
Verbal-Numerical Reasoning	4.5×10^{-36}	.418	.379	67,558
Alcohol Intake Frequency	8.1×10^{-29}	.231	.093	44,307
Risk-Taking	9.3×10^{-25}	.291	.115	52,388
Neuroticism	2.2×10^{-24}	.139	.092	30,306
Tobacco Use	4.2×10^{-21}	.485	.333	74,809
Height	8.7×10^{-20}	.081	.030	20,147
Depressive Disorder	2.2×10^{-13}	.033	.112	10,158
Age, Years	5.8×10^{-9}	.177	.026	36,443
Alcohol Dependency	4.5×10^{-6}	.175	.208	36,101
Anxiety Disorder	2.8×10^{-4}	.116	.062	26,355
Visual Acuity	.005	.001	.029	792
Bipolar Disorder	.007	.117	.037	26,551
Hand Grip Strength	.024	.494	.002	75,689
Menstruation at Assessment	.115	.051	.025	14,128
No. of Cancers	.127	.131	.002	28,929
Schizophrenia	.162	.257	.053	47,870
Year of Assessment	.159	.036	.001	10,871
Sex of Child	.234	.010	.062	4085

Significance threshold set at $p < 2.1 \times 10^{-4}$.
SNP, single nucleotide polymorphism.

Individuals with many risk alleles for ADHD were more likely to have higher BMI than those with few risk alleles. There is limited research investigating why ADHD and high BMI often co-occur, but our findings, together with recent findings using LDSR (1,35), suggest that they have an overlapping genetic basis. Further research is needed to identify genetic pathways and neurobiological mechanisms relating to this genetic overlap, which could prove vital for improving prevention and treatment interventions for individuals with ADHD who are at risk of obesity. One possibility is that dopaminergic pathways and pathways implicated in eating patterns (e.g., binge- and emotional-eating), sleeping patterns, and sedentary behavior explain the association between ADHD and BMI, which would be in line with initial evidence (42–46). The common mechanisms underlying both ADHD and BMI could either reflect biological pleiotropy, where similar mechanisms influence both traits, or mediated pleiotropy, where certain mechanisms influences one of the traits, which in turn influences the other.

Polygenic risk for ADHD was significantly associated with lower cognitive ability, which is in line with previous twin and molecular genetic studies (2,29,30,35). The association between ADHD and general cognitive ability is thought to be mainly driven by ADHD symptoms that influence IQ, at least in adolescence (47). It may therefore be possible that there are common biological mechanisms underlying both ADHD and IQ, but perhaps also certain biological mechanisms underlie ADHD, which in turn influences IQ, possibly through poor educational achievement owing to difficulties concentrating in school (47,48).

Polygenic risk for ADHD significantly and positively predicted neuroticism, including individual items such as mood swings and irritability. Two recent studies failed to find any genetic correlation between ADHD and neuroticism using LDSR (35,49). The discrepancy in findings may be due to the previous studies having smaller sample sizes or the use of LDSR rather than polygenic scoring, potentially resulting in insufficient statistical power to detect effects.

PRSs for ADHD also predicted depression, and anxiety at a suggestive level, which is in line with findings from twin and genome-wide studies (9,31–33,35). The ADHD PRSs did not predict BD or schizophrenia; however, these results should be considered with caution because previous family-based and

genome-wide studies using other statistical methods have reported significant genetic associations between these disorders (34,35). The discrepancy in findings may be related to the older age of our sample, the use of a population cohort rather than clear case-control groups, or insufficient power to detect effects, in particular for schizophrenia (288 cases) based on power calculations using Avengeme R package (power for analyses: BD = 0.99, schizophrenia = 0.22). Further polygenic studies are needed to investigate the association of ADHD with BD and schizophrenia across different study populations to clarify the true etiological relationship between the disorders.

Individuals with many risk alleles for ADHD were more likely to display alcohol dependency, have higher alcohol intake frequency, and be smokers and risk-takers compared with those with few risk alleles. Previous genome-wide studies reported significant genetic associations between ADHD and smoking (35,50,51) but not between ADHD and alcohol use (52), and no studies to our knowledge have investigated the genetic association between ADHD and risk-taking. The shared genetic risk between ADHD and these risk-taking and health-related outcomes may be explained by common neurobiological mechanisms involved in self-regulation and inhibitory control. Further research targeting relevant genes and pathways is needed to test such hypotheses.

Overall, our findings lend support for the continuous nature of ADHD across the entire population. We find that common risk alleles that contribute to clinically diagnosed ADHD also influence common traits and disorders in the general population, across ages, which suggests that ADHD symptoms represent continuous traits and that similar genetic influences may be present in younger and older individuals. This fits well with the current understanding of ADHD based on evidence from behavioral, family-based, and genetic studies (53–55).

To investigate if our significant results could be the result of type I errors, we examined if PRSs for ADHD significantly predicted several "control" phenotypes that were not expected to be associated with polygenic risk for ADHD. Out of the eight "control" traits, only age was significantly predicted by ADHD PRS. It is possible that this association is caused by some real effect, such as genetic influences on ADHD being stronger during certain developmental periods, for example in childhood, when the prevalence of ADHD is the highest. Twin studies suggest that the heritability of childhood ADHD is stronger than in adult ADHD, but this may also be due to rater effects (56). Hypothetically, this would then have been captured in the discovery GWAS, where genetic effect sizes in children would be larger than in adults and in turn lead to PRS associations with younger age in the UK Biobank. However, we cannot rule out the possibility that the "age" result reflects a false positive or is related to the overlap between UK Biobank participants and those of the Psychiatric Genomics Consortium/iPSYCH ADHD GWAS, which may cause slight inflation in results. It is reassuring, however, that seven of eight control traits showed nonsignificant results and that the relative strength of the significant results are in line with other preliminary genetic findings.

An advantage of using a large dataset and the PRS approach is that we could directly investigate sex differences in the relationship between PRSs and the target phenotypes. A recent study based on the ADHD mega GWAS data found a strong genetic correlation for ADHD across sex and no difference in polygenic load across sex (36), and we extend these findings to show that the polygenic influences underlying the relationship between ADHD and co-occurring features are similar across men and women.

Limitations and Future Directions

One should interpret our findings in light of the study limitations. Our study participants were between 40 and 73 years of age, had a lower prevalence of mental health disorders, and were recruited within the United Kingdom. It would be informative to investigate the generalizability of our findings by replicating the analyses using participants of different age groups and from different populations. Selection bias of the sample could also have influenced the associations we report (57); however, we controlled for several important measures, including age and birthplace, to minimize the chance for bias. In addition, several of the significant genetic associations that we identified confirm previous statistical genetic findings (35), offering some validation of our results. PRSs explain only a tiny fraction of the variance in the target phenotypes, and obtaining a complete picture of the etiological overlap between ADHD and co-occurring features will require larger sample sizes and inclusion of other genetic factors, such as copy number and rare variants.

In conclusion, higher polygenic load for clinical ADHD was associated with higher BMI, neurotic and risk-taking behavior, anxiety and depressive disorders and substance use, and lower general cognitive ability in the general population. These findings suggest that the co-occurrence of several traits and disorders with ADHD are partly explained by the same common genetic factors. Further investigations are needed to determine the specific neurobiological mechanisms associated with the shared genetic etiology between ADHD and co-occurring features.

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ARTICLE INFORMATION

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CHAPTER 5 – Autonomic arousal profiles in young individuals with ADHD as a function of recording context

5.1 Abstract

A recent study (James et al., 2016) found that attention-deficit/hyperactivity disorder (ADHD) was associated with hypo-arousal, indexed by low electrodermal activity, during a low-demand reaction-time task, which normalised in a fast-incentive condition. We now investigate if (1) autonomic arousal in individuals with ADHD changes over a long testing session and (2) across time, to clarify if arousal profiles are context-dependent. We also examine (3) how autonomic arousal relates to each ADHD symptom domain, and specificity of arousal profiles to ADHD, by controlling for oppositional defiant/conduct disorder (ODD/CD) symptoms. Skin conductance level (SCL) and non-specific fluctuations (NSFs) were measured during four successive resting-state and cognitive conditions from 71 adolescents/young adults with ADHD and 140 controls. Lower arousal was observed in individuals with ADHD only during a slow, low-demanding task, and more fluctuating arousal was observed towards the end of assessment. Both inattentive and hyperactive-impulsive symptoms were associated with arousal levels and fluctuations, independently from ODD/CD. Overall, we extend previous findings showing that under-arousal, but also fluctuating arousal, are context-specific rather than stable impairments in ADHD.

5.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with postulated links to hypo-arousal and arousal dysregulation. The state regulation and cognitive-energetic accounts suggest that a sub-optimal arousal state in ADHD may lead to inconsistent cognitive performance, reflected for example by within-subject fluctuations in reaction time (van der Meere, 2005; Sergeant, 2005). Recent initial findings from our research group have suggested that hypo-arousal, while observed during performance on a low-demand reaction time task, is not stable in individuals with ADHD but may be normalised during more stimulating tasks (James et al., 2016). More research is needed to understand the physiological underpinnings of ADHD by exploring whether ADHD case-control differences are context-dependent or stable across time, and whether these differences are specific to ADHD or can be explained by other related behaviours.

Skin conductance (SC) provides an objective and reliable index of arousal in the peripheral nervous system (Boucsein, 2012). SC is a measure of electrodermal activity, which is stimulated by the autonomic sympathetic nervous system, a system involved in regulating arousal and alertness (Boucsein, 2012; Critchley, 2002). In this study, we use the term 'arousal' to describe changes in electrodermal activity. Skin conductance level (SCL) represents the tonic level of arousal (average level) and non-specific fluctuations (NSFs) represent a phasic (transient) change in arousal. Increased SCL indexes an increase in peripheral arousal (Boucsein, 2012), whereas increased non-specific fluctuations indicate more variability in arousal.

Several studies have reported attenuated SCL in children with ADHD, compared to controls, indicating hypo-arousal during resting-state (eyes open and eyes closed) and task conditions (Barry et al., 2012; Conzelmann et al., 2014; Dupuy, Clarke, Barry, Selikowitz, & McCarthy, 2014; Iaboni, Douglas, & Ditto, 1997; Lazzaro et al., 1999; Mangeot et al., 2001; Mangina, Buezeron-Mangina, & Grizenko, 2000; O'Connell, Bellgrove, Dockree, & Robertson, 2004). Research is more limited in adults, where

study findings across resting-state and task conditions are inconclusive in terms of hypo-arousal in ADHD (Hermens et al., 2004; Mayer, Wyckoff, & Strehl, 2016). Mixed findings, mainly from studies on younger children and adolescents with ADHD, have emerged also for NSFs. While several studies on children and adolescents with ADHD reported significantly fewer NSFs in their electrodermal activity during resting conditions than controls (Beauchaine, Katkin, Strassberg, & Snarr, 2001; Crowell et al., 2006; Satterfield & Dawson, 1971), other studies in children have not replicated these findings (Beauchaine et al., 2015) and one study even found the opposite direction of effects in a resting condition while participants listened to 40-decibel white noise (Pliszka, Hatch, Borcherding, & Rogeness, 1993). Further research is needed using large samples, across testing conditions, to clarify these inconsistencies in the literature.

Our understanding is also limited regarding the specific aspects of ADHD that arousal measures tap into. Only one study, which consisted of girls with and without ADHD, has explored the relationship between SCL and the two ADHD symptoms domains separately, reporting that lower SCL was strongly correlated with higher inattentive symptoms (r = -0.45) and weakly-to-moderately correlated with hyperactive-impulsive (r = -0.23) symptoms, in individuals with and without ADHD (Dupuy et al., 2014). No study to our knowledge has explored this with NSFs, and the relationship between SCL and NSFs remains poorly understood. Studies in children have reported that NSFs correlate positively with average SCL (Burch & Greiner, 1960; Silverman, Cohen, & Shmavonian, 1959); yet neuroimaging and electrophysiological studies suggest that NSFs and SCL index different underlying processes (Lazzaro et al., 1999; Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004).

In a recent investigation with a large sample of adolescents and young adults, we found that individuals with ADHD displayed autonomic under-arousal during a baseline (slower, non-rewarded) task condition of a four-choice reaction time called the Fast Task, but this was normalised in a more stimulating fast-incentive condition (James et al., 2016). These findings support an arousal dysregulation account of ADHD rather

than suggesting that individuals with ADHD display stable hypo-arousal. Further support for this view comes from a study that investigated autonomic arousal measures in participants during a sustained attention to response task before and after taking part in either self-alert training, where participants learned to modulate their arousal levels, or placebo training (O'Connell et al., 2008). Results showed that both ADHD and control participants had increased specific skin conductance responses, indicating increased phasic arousal, after the alertness training. Another study in a healthy population sample found increased SCL during a continuous performance task compared to baseline, a difference defined as 'activation', which further suggests context-dependent effects of autonomic arousal (Vaez Mousavi, Barry, & Clarke, 2009). We now investigate context effects in ADHD further by studying tonic (SCL) and phasic (NSF) autonomic arousal across a longer experimental assessment, to improve our understanding of the stability of autonomic arousal profiles in ADHD.

In this study we firstly aim to (1) extend initial findings from James et al., (2016) and investigate if ADHD case-control differences in both tonic arousal, indexed by SCL, and phasic arousal, indexed by NSF, vary across a long testing session consisting of a combination of resting-state and task conditions (Resting-state time 1, CPT-OX, Fast Task, Resting-state time 2) commonly used in ADHD research, in a large sample of adolescents and young adults. We then more specifically aim to (2) examine if ADHD case-control differences in arousal measures vary across time from Resting-state time 1 to time 2. These findings may provide insight on whether low levels and fluctuating arousal in ADHD reflect context-specific states or stable traits, which in turn would be relevant both for our understanding of the biological underpinnings of ADHD and potentially for treatment. Thirdly, to further understand which aspects of ADHD specifically tap into tonic and phasic arousal, we aim to investigate (3) how arousal measures are associated with each of the ADHD symptom domains of inattention and hyperactivity/impulsivity.

In all analyses, we also aim to investigate if associations between ADHD and arousal are independent of oppositional defiant disorder and conduct disorder (ODD/CD) symptoms, which frequently co-occur with ADHD and have previously been associated with lower SCL and skin conductance responses (Delamater & Lahey, 1983; Fung et al., 2005; Posthumus, Bocker, Raaijmakers, Van Engeland, & Matthys, 2009). One small study of males found that among individuals with ADHD, those with and without comorbid CD showed similar profiles of fewer NSFs during a baseline resting condition compared to controls (Beauchaine et al., 2001); however, more powerful studies including both males and females are needed to determine the specificity of arousal profiles in ADHD.

5.3 Materials and methods

5.3.1 Participants

The original sample (before quality control and exclusions) consisted of 275 participants, followed-up on average 5.8 years (SD = 1.1) after initial assessments. At follow-up, participants were on average 18.0 years of age (age range: 11.1-25.9). 108 participants had a diagnosis of DSM-IV combined type ADHD in childhood (9 sibling pairs, 90 singletons) and 167 were controls (74 sibling pairs, 19 singletons).

Participants with ADHD were initially recruited from ADHD clinics in south-east England (Kuntsi et al., 2010). Diagnosis of DSM-IV combined type ADHD was established using the Parental Account of Childhood symptoms (PACS), a semi-structured interview with high inter-rater reliability (Chen et al., 2008). Controls were recruited from schools in the same region and were age and sex matched with the clinical sample. All participants were aged between 6 and 17 at initial assessment. Exclusion criteria were: IQ<70, autism, epilepsy, general learning difficulties, brain disorders and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. At follow up, six controls met DSM-IV ADHD criteria based on parent-ratings on the Barkley Informant Rating Scale (Barkley & Murphy, 2006); these

participants were excluded from analyses. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

SC data were available for 221 participants (mean age: 17.7 years, age range: 11.9-23.3), out of our original sample of 256, as SC data collection equipment did not arrive until after the initial participants had been assessed. We additionally excluded participants within each testing condition who experienced SC equipment failure or extreme drowsiness. The final sample consisted of 71 ADHD probands ('ADHD persisters') and 140 controls. The ADHD and control groups did not differ in age (t = .20, p = .66), gender ($\chi 2$ = .63, p < .43), but did differ on IQ scores (t = -7.47, p < .001) (Table 5.1).

5.3.2 Materials and procedure

Participants with childhood ADHD were classified as having ADHD if they met DSM-IV criteria for ADHD at follow-up. If they scored a 'yes' on ≥ 6 items in either the inattention or hyperactivity-impulsivity domains of the Diagnostic Interview for ADHD in adults (DIVA) (Kooij & Francken, 2007) and if they scored ≥ 2 on two or more areas of impairments from the Barkley's functional impairment scale (BFIS) (Barkley & Murphy, 2006), they were classified as ADHD persisters at follow-up. Out of the 108 participants with childhood ADHD, 23 were classified as ADHD 'remitters' at follow-up and were not included in this study.

Conners' Parent Rating Scale – Revised (L): is a questionnaire measure used to assess internalizing and externalizing behavior from children and adolescents based on parent ratings. The scale includes 18 statements that measure DSM-IV inattentive and hyperactive-impulsive ADHD symptoms (Conners, 1997). Each statement is rated on a three-point scale, by parents, and the highest possible score is 54. These subscales were used in the correlation analyses as they were assessed in both ADHD cases and controls.

The Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000): is a structured interview administered by lay interviewers. The K-section of the DAWBA questionnaire, which measures 'behaviours which sometimes gets children into trouble', was administered to participants. These items reflect current symptoms, closely related to DSM-IV diagnoses of ODD and CD (Heiervang et al., 2007; Goodman et al., 2000). Ten items were administered to participants, each rated from 0 to 2, and the total sum of scores were calculated for each participant.

IQ: The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) were administered to derive an IQ estimate (Wechsler, 1999).

Resting-state with eyes open: Participants were asked to keep as still as possible while resting in a chair with their eyes open before and after the cognitive assessments. They were encouraged to find a spot on the wall in front of them where they could fixate their gaze. The resting-state sessions each lasted for 3 minutes.

The Fast Task; baseline condition (Andreou et al., 2007): The baseline condition of the Fast Task consists of 72 trials, which followed a standard warned four-choice RT task. Four empty circles (warning signals, arranged horizontally) first appeared for 8s, after which one of them (the target) was colored in. Participants were asked to press the response key that corresponded to the target position. Following a response, the stimuli disappeared and a fixed inter-trial interval of 2.5s followed. Speed and accuracy were emphasized equally. If participants did not respond within 10s, the trial terminated.

The cued flanker Continuous Performance Task (CPT-OX): This CPT-OX (Doehnert et al., 2008; Valko et al., 2009) includes rare cued Go and NoGo conditions embedded in a vigilance task with frequent distractors to assess attentional and inhibitory processes. The test consists of 400 letters presented for 150ms with a stimulus onset asynchrony of 1.65s in a pseudo-randomized order. The cue letter O occurred with 20% probability

(80 Cue stimuli), signaled a Go–NoGo task, and induced response preparation. Participants pressed a mouse button as fast as possible every time the cue was followed directly by the letter X (O-X) target sequence, 10% probability, 40 Go stimuli] but had to withhold responses to O-not-X sequences (NoGo trials, also 10%, 40 NoGo stimuli).

5.3.3 Procedure

Participants were re-contacted by telephone and scheduled for a follow-up clinical interview and cognitive assessments at our research centre while electrodermal and electroencephalogram (EEG) measures were recorded. Before the cognitive assessments, participants were asked to remain still and rest with their eyes open while fixating at a point in front of them for 3 minutes. They then performed the CPT for 11 minutes, followed by the Fast Task baseline condition for 13 minutes, and were asked to rest again with their eyes open for 3 minutes at the end of the testing session. A 48-hour ADHD medication-free period was required and the participants were also asked to abstain from caffeine, smoking, and alcohol on the day of testing.

5.3.4 Skin conductance

Skin conductance response was recorded using PSYCHLAB SC5 24 bit equipment system, which has an absolute accuracy of +/- 0.1 microsiemens. The SC5 is connected to a computer that runs the PSYCHLAB software where the data can be monitored and recorded in real time and parameters can be set. SC was measured by attaching a pair of 8mm diameter silver-silver chloride electrodes on the palm of participants' non-dominant hand (thenar eminence and hypothenar eminence) at the beginning of the cognitive test battery. An electrode paste, formulated with 0.5% saline in a neutral lotion/cream style base (provided by PSYCHLAB), was used to establish a stable electrical SC signal. The SC5 is DC coupled (infinite time constant), and a constant imperceptible voltage (0.5V) was applied. SC5 automatically calibrates itself when switched on and then runs at a fixed internal sample rate of 80Hz and an additionally 10Hz filter is applied to response signal to prevent aliasing.

SC variables were calculated using a system that is based on a SC sigmoid-exponential model that allows the tonic measure of SCL to be disentangled from phasic SC fluctuations and allows the decomposition of overlapping SC fluctuations (Lim et al., 1997). The statistical model was applied to each task condition. Each participant's data were inspected visually by a researcher to confirm that the data were scored properly using the statistical model. Each NSF reflects a rise in SCL for at least 500 milliseconds followed by at least 300 milliseconds of non-rising SC, and the minimum amplitude of the NSFs was set to 0.02 microsiemens. The number of NSFs per second was used as the final measure to control for minor individual differences in recording lengths. Mean SCL and NSFs per second were calculated for each participant in each testing condition. We examined average measures of SCL and NSFs across task performance in the CPT-OX and Fast Task, and did not exclude event-locked SC variables, as event codes during the CPT-OX were not retrievable in these data.

5.3.5 Data Analysis

We ran regression models to investigate ADHD case-control group differences in SCL and NSF measures within each testing condition (Resting-state time 1, CPT-OX, Fast Task, Resting-state time 2). Relatedness between sibling pairs was controlled for by using the 'robust cluster' command in STATA (StataCorp, College Station, TX). Random-intercept linear models were used to test the main and interaction effects of group (ADHD cases, controls) and time (Resting-state time 1, Resting-state time 2) on SCL and NSFs, to examine the change in autonomic arousal in ADHD and control groups over time. Random-intercept models control for clustered data, due to relatedness between siblings, and handle missing data using the maximum likelihood method, which in turn reduces the loss in power from missing data points. We re-ran all analyses controlling for ODD/CD symptoms to examine if any identified ADHD case-control differences could be explained by co-occurring ODD/CD symptoms.

We ran linear regression models to investigate the associations of SC measures with inattentive and hyperactive-impulsive symptoms, respectively, and added an interaction term (SC*ADHD group) to investigate if the strength of the associations

were different in the ADHD and control groups. We tested these associations only in conditions that showed sensitivity to ADHD as indicated by a significant case-control difference in SC measures. We re-ran all analyses controlling for ODD/CD symptoms.

We re-ran the main analyses on ADHD case-control group comparisons with IQ added as a covariate to examine its potential effects. We further ran sensitivity analyses testing age and gender as covariates in the main analyses in line with previous analyses in the same sample (Kitsune et al., 2015). The effects of potential longer-term use of medication on SC measures were examined by running SC comparison tests between unmedicated and medicated participants with ADHD.

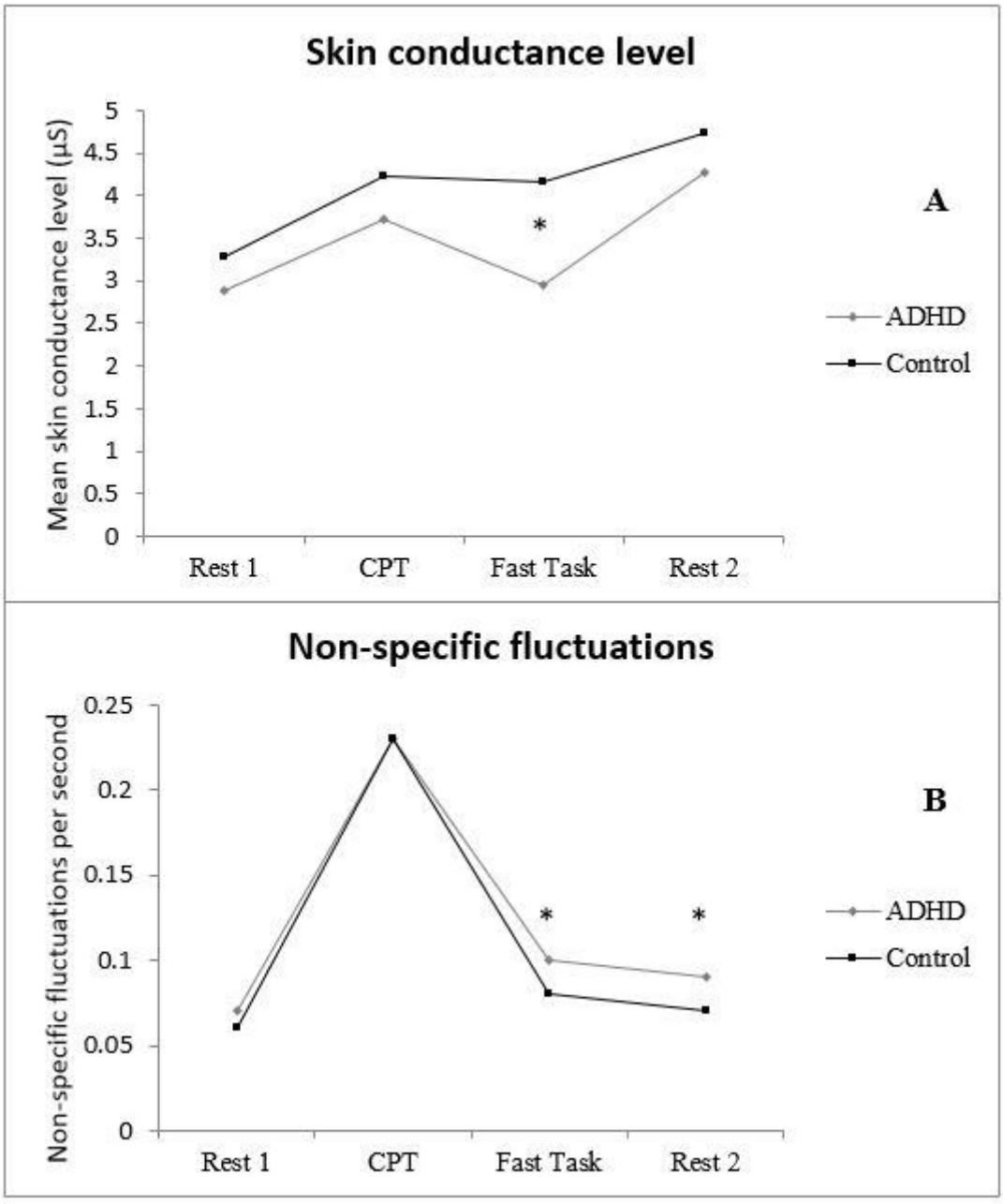
5.4 Results

5.4.1 ADHD case-control differences in arousal across testing sessions

Pairwise comparisons revealed no significant differences ($p > .05$) between the ADHD and control groups in NSFs or SCL during the two initial testing conditions (Resting-state time 1 and CPT-OX task performance; Figure 5.1). During performance on the Fast Task and Resting-state time 2, individuals with ADHD showed significantly more NSFs than the control group. There was no significant group difference in SCL during Resting-state time 2, in contrast to the significantly lower SCL found during the Fast Task, as reported James et al. (2016) (Figure 5.1, Table 5.1).

Individuals with ADHD had a significantly higher level of ODD/CD symptoms (M = 4.03, SD = 2.63) than individuals in the control group (M = 1.61, SD = 1.90; $t(210) = 6.87$, $p < .001$). After controlling for ODD/CD symptoms in the models, SCL findings of case-control differences did not change but NSF findings during the Fast Task changed slightly, in regards of the effect size (Cohen's d: from .33 to .27) and *p*-value (from .04 to .07) (Table 5.1), although an overlap in 95% confidence intervals of coefficients indicated that the change in results was not significant (95% CI [0.01, 0.70] to [-0.17, 0.17]).

Figure 5.1 Mean skin conductance level (A) and non-specific fluctuations (B) for ADHD and control groups in each testing condition



Note: Data on SCL from the Fast Task have already been presented (James et al., 2016), but for ease of comparison, results specific to this analysis have been replicated here with the additional results across other task conditions.

**p-value < .05 for comparison between ADHD-control groups. CPT: continuous performance task. ADHD: Attention-deficit/hyperactivity disorder group.*

Table 5.1 Descriptives and pair-wise comparisons between Groups (ADHD, control) in each condition on skin conductance measures

		ADHD (71)	Control (140)	t/χ^2	*p*	d	d Cov: ODD/CD
Male sex, n (%)		59 (83%)	107 (76%)	.63	.43	.17	
IQ, *M* (*SD*)		95.38 (14.97)	110.08 (12.69)	7.47	.001	-1.03	
Age, *M* (*SD*)		17.70 (2.83)	17.75 (2.28)	.20	.66	.02	
Rest time 1	*SCL*	2.88 (2.07)	3.29 (2.26)	-1.43	.31	-.20	-.18
	NSF/s	.07 (.05)	.06 (.06)	.33	.74	.05	.01
CPT	*SCL*	3.72 (2.16)	4.24 (2.68)	-.96	.32	-.13	-.09
	NSF/s	.23 (.13)	.23 (.13)	.02	.98	.01	.01
Fast Task	*SCL*	2.96 (2.05)	4.16 (1.91)	-3.44	<.01	-.49*	-.56*
	NSF/s	.10 (.04)	.08 (.04)	2.06	.04	.33*	.27
Rest time 2	*SCL*	4.28 (2.23)	4.73 (2.77)	-.41	.69	-.06	-.01
	NSF/s	.09 (.06)	.07 (.06)	2.14	.03	.32*	.30*

Note. Data on SCL from the Fast Task have already been presented (James et al., 2016), but for ease of comparison, results specific to this analysis have been replicated here with the additional results across other task conditions.

**p-value < .05. d: Cohen's d. Cov: Covariate included in models. CPT: Continuous performance task. SCL: Skin conductance level. NSF/s: Non-specific fluctuations per second. ADHD: Attention-deficit/hyperactivity disorder group. ODD/CD: Oppositional defiant disorder/Conduct disorder symptoms.*

5.4.2 ADHD case-control differences in arousal across time

The random-intercept models revealed significant main effects of time (Resting-state time 1 vs 2) on NSFs and SCL (Table 5.2), showing that NSFs and SCL significantly increased over time. We found no significant main effect of group (ADHD vs control) or group-by-time interaction effects on NSFs or SCL (Table 5.2). When ODD/CD symptoms were controlled for, the group-by-time interaction effect became significant for NSFs (z = 2.00, p = .045). Post-hoc analyses when controlling for ODD/CD symptoms revealed significant increases in NSFs from resting-state time 1 to time 2 in the ADHD group (t = 3.32, p = .002), but not in the control group (t = 0.63, p = 0.53).

As the group-by-time interaction effect on NSFs emerged as significant after controlling for ODD/CD symptoms, we decided to run regression analyses to explore the associations between ODD/CD symptoms and SC measures, within each group (ADHD, control) and each condition. We found no significant associations between ODD/CD symptoms and SC in any of the groups or conditions (Table S1).

Table 5.2. Main effects of Group (ADHD vs Control), Time (Resting-state time 1 vs 2) and interaction effects of Group-by-Time on skin conductance measures

	Skin conductance level		**Non-specific fluctuations**	
	z	*p*	*z*	*p*
Group	-0.94	.35	1.61	.11
Time	8.91	.001*	2.71	.01*
Group*Time	0.38	.71	1.53	.12*

** p < .05 after controlling for ODD/CD.*

5.4.3 Linear associations between arousal measures and each ADHD symptom domain

Linear regression models revealed that NSF recorded during the Fast Task was significantly and positively associated with hyperactive-impulsive symptoms in the full sample, and NSF during Resting-state time 2 was significantly and positively associated with both inattentive and hyperactive-impulsive symptoms (Table 5.3). SCL recorded during the Fast Task was significantly and negatively associated with both symptom domains. While NSF during the Fast Task was not significantly associated with inattentive symptoms in the full sample, the NSF-by-group interaction was significant, revealing that the association between NSF and inattentive symptoms was significant in the ADHD group (*Beta* = .13, *p* = .01), but not in the control group (*Beta* = -.01, *p* = .77). No other interaction terms (SC*group) were significant (Table 5.3). When we controlled for ODD/CD symptoms in the regression models, the pattern of results did not change with regard to significance level (Table 5.3).

Table 5.3 Main associations between skin conductance level and non-specific fluctuations with ADHD symptom domains and skin conductance-by-group (ADHD, control) effects on ADHD symptom domains

	Fast Task								**Resting-state time 2**			
	Non-specific fluctuations (NSF)				**Skin conductance level (SCL)**				**Non-specific fluctuations (NSF)**			
	Main association		Interaction (NSF*group)		Main association		Interaction (SCL*group)		Main association		Interaction (NSF*group)	
	B	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*
H/I	**.20**	**<.01***	-.06	.66	**-.26**	**<.01***	-.15	.19	**.18**	**.02***	-.01	.98
IN	.10	.19	**-.12**	**.04***	**-.26**	**<.01***	-0.10	.10	**.18**	**.02***	-.02	.77

Note: Associations between ADHD symptoms and arousal measures were only tested during the conditions that revealed significant case-control differences in arousal.
** p < .05 after controlling for ODD/CD. H/I: Hyperactivity/Impulsivity symptoms. IN: Inattentive symptoms.*

5.4.4 Sensitivity analyses

We re-ran the main pairwise comparisons of groups (ADHD vs Control) with IQ added as a covariate (Table S2). We found that the pattern of results remained the same for NSFs but for SCL the ADHD case-control difference during the Fast Task was no longer significant and the effect size (Cohen's d) changed from -.49 to -.09 (Table 5.1), although 95% CI's showed an overlap before and after controlling for IQ (95% CI [-0.95, -0.28] to [-0.58, 0.15]).

Due to the changes in results after controlling for IQ in the SCL analyses (Table S2), we ran additional sensitivity analyses to investigate the associations between IQ and SC measures across conditions (Table S3). Linear regression models revealed significant (p < .05) and positive associations between SCL and IQ (*Beta* = .17-.40) in all four testing conditions. The interaction terms (SCL*group) were not significant in any conditions, revealing that associations were similar across groups. We found no significant associations between NSF and IQ (Table S3).

We further re-ran the main pairwise comparisons of groups (ADHD vs Control) with age and gender added as covariates and found that the pattern of findings remained the same in terms of significance of findings (Table S4). We also ran SC comparison tests between unmedicated and medicated participants with ADHD to investigate the long-term effects of medication. Short-term effects of medication were controlled for, as participants were asked to have a 48-hour medication-free period before testing. There were no significant differences in SCL ($t(34) = .68$, $p = .50$) or NSF ($t(35) = -.48$, $p = .64$) between unmedicated and medicated participants.

As we found significant ADHD case-control differences in SC during the 13-minute long Fast Task but not during the 11-minute long CPT, we aimed to explore whether the significant differences during the Fast Task emerged because of the longer testing session, rather than the order or nature of the task. James et al. (2016) previously demonstrated that the significant ADHD case-control difference in SCL during the Fast

Task (baseline condition) was consistent across time, as significant differences were found in each 4-minute long snippet of the task. Here, we extracted NSF data during the first 11 minutes of the Fast Task to match the CPT on task length, and re-ran the ADHD case-control comparisons. We found that the ADHD case-control difference in NSFs during the Fast Task was reduced to trend level when using the shorter 11-minute time period (*Beta* = .03, *p* = .068).

5.5 Discussion

In this large study of 211 adolescents and young adults, we found that autonomic arousal profiles of individuals with ADHD varied across testing conditions. First of all, ADHD case-control differences in tonic arousal, indexed by SCL, only emerged during a slow and low-demanding cognitive task. Case-control differences in phasic arousal, indexed by NSF, emerged towards the end of the assessments, during the low-demanding cognitive task and the final resting-state condition (time 2). Further analyses showed that case-control differences in phasic arousal, but not tonic arousal, emerged over time from resting-state time 1 to time 2, once ODD/CD symptoms were controlled for. Lastly, both ADHD symptom domains were significantly associated with lower levels of tonic arousal and more fluctuating arousal, independently of ODD/CD symptoms. Overall, our findings suggest that individuals with ADHD experience difficulties regulating their arousal rather than being constantly under-aroused. Inconsistent findings in the literature on autonomic arousal in ADHD might be explained by differences in experimental designs and tasks.

Extending the initial report from James et al. (2016), we now show that tonic autonomic arousal, measured by SCL, did not remain significantly lower in individuals with ADHD compared to controls beyond the slow, baseline condition of the Fast Task; during resting-state conditions and CPT-OX task performance. These findings suggest that lower arousal levels in individuals with ADHD may be especially salient during slow and low-demanding tasks compared to faster-paced and more demanding tasks such as the CPT or the fast-incentive condition of the Fast Task (as demonstrated in James

et al., 2016). It is also possible that the lower arousal level in the ADHD group during the Fast Task, but not the CPT condition, was due to fatigue effects as the Fast Task followed the CPT in the order of tasks. We were unable to separate fatigue effects from effects of cognitive demand, as the tasks were not counterbalanced in this experiment. Our analyses further revealed that lower tonic arousal during the Fast Task, where case-control differences were identified, was associated with a higher level of inattentive and hyperactive-impulsive symptoms, supporting initial findings from a study only in girls (Dupuy et al., 2014). Our finding suggests that individuals with ADHD may experience difficulties in regulating their arousal levels rather than experience constant hypo-arousal, which implies that arousal is malleable in individuals with ADHD and may therefore be suitable as a potential treatment target. Our findings further suggest that inconsistencies in the literature (Hermens et al., 2004; Mayer et al., 2016) may be explained by the different experimental paradigms used across studies.

We further found that individuals with ADHD displayed significantly more fluctuating arousal, indexed as a higher number of NSFs per second, compared to controls, during the two final testing conditions (the Fast Task and Resting-state time 2) only. These findings suggest that arousal variability in ADHD, similarly to under-arousal, may become more salient during slower and low-demanding tasks, but also towards the end of assessment, over time. This is further supported by our sensitivity analysis showing that the ADHD case-control difference in NSFs during the 13-minute long Fast Task was no longer significant when we shortened the task to match the 11-minute long CPT. These findings indicate that more fluctuations in ADHD may become especially salient over time, possibly in combination with the low-demanding task.

Our results further showed that the fluctuations in and level of arousal increased over time, from resting-state time 1 to time 2. When we tested the group-by-time interaction on fluctuations, the effect emerged as significant once ODD/CD symptoms were controlled for and post-hoc analyses revealed than the fluctuations in arousal

increased over time only in the ADHD group. These findings further suggest that fluctuating arousal profiles in ADHD, relative to controls, become more salient over time; an effect that is enhanced by controlling for other co-occurring externalizing behaviours.

NSFs were associated with both inattentive and hyperactive-impulsive symptoms, across groups, in the testing conditions that showed case-control differences, with the only exception of the Fast Task where NSFs and inattention were only significantly associated in the ADHD group. Overall, we found that individuals with ADHD did not show stable abnormalities in fluctuating arousal, similarly to under-arousal, which may in turn explain highly inconsistent findings in the literature where different experimental designs have been used. The direction of effects is in line with findings from one previous study that showed a trend of more NSFs in children with ADHD compared to controls (Pliszka et al., 1993), but is inconsistent with other studies of children and adolescents which have found opposite effects of less frequent NSFs in individuals with ADHD (Lazzaro et al., 1999; Satterfield & Dawson, 1971). Further research across different experimental conditions and age groups, is therefore needed to clarify the discrepancy in findings.

This is the first larger study, to our knowledge, to investigate the specificity of both phasic and tonic arousal profiles in young adults with ADHD by controlling for ODD/CD symptoms in analyses. ODD/CD symptoms did not account for our findings on atypical tonic arousal profiles in ADHD, which is in line with previous research (Beauchaine et al., 2001; van Lang et al., 2007). For phasic arousal, ODD/CD symptoms did not account for the associations with ADHD, however, the group-by-time effect emerged as significant after controlling for ODD/CD symptoms. This suggests that controlling for ODD/CD symptom enhances the relationship between phasic arousal and ADHD over time, but it is not clear from these results how ODD/CD symptoms relate to the other variables, as they (a) do not account for the linear associations between NSFs and ADHD symptom domains (Table 5.3) and (b) are not significantly associated with NSFs

(Table S1). While previous research has suggested that individuals with antisocial/conduct problems have smaller amplitude of specific skin conductance responses (Delamater & Lahey, 1983), less is known of non-specific fluctuations. Further studies are needed to clarify the complex relationship between ODD/CD, NSFs and ADHD, to determine the specificity of fluctuating arousal profiles in ADHD.

We further showed that individuals, regardless of ADHD diagnosis, who had lower levels of tonic arousal also tended to have lower IQ scores and that the ADHD case-control difference in tonic arousal was mainly accounted for by IQ. These intriguing findings suggest that it is important that IQ is taken into consideration in future studies that investigate arousal levels in ADHD and that any potential mediating variables are explored further.

A limitation of this study is that we used measures of NSF averaged across each of the CPT-OX and Fast Task conditions, as we were unable to retrieve event codes. This means that we could not tease apart SC fluctuations during stimuli presentation and response execution from SC fluctuations during no task events. It would have been interesting to study both event-specific and non-specific fluctuations separately to explore how they each are implicated in ADHD, however, given that very few studies have investigated arousal variability in ADHD, we believe it is still meaningful to study average fluctuations in our rich dataset that spans across a long testing session.

5.6 Conclusion

We found that adolescents and young adults with ADHD displayed lower levels of and more fluctuating autonomic arousal under certain experimental conditions. ADHD case-control differences in tonic arousal emerged only during a slow, low-demanding cognitive task. A case-control difference in phasic arousal was also observed during the low-demanding task and also towards the end of the assessment. We further found that tonic and phasic arousal were associated with both inattentive and hyperactive-impulsive symptoms, independently of ODD/CD symptoms. Our findings suggest that

both tonic and phasic autonomic arousal profiles in ADHD are context-specific rather than representing stable impairments. Our findings also highlight how inconsistent findings in the ADHD literature on arousal may be explained by differences in experimental paradigms used across studies.

CHAPTER 6 – Beneficial effects of acute high-intensity exercise on electrophysiological indices of attention processes in young adult men

6.1 Abstract

Background: Emerging research suggests that a single bout of aerobic exercise can improve cognition, brain function and psychological health. Our aim was to examine the effects of high-intensity exercise on cognitive-performance and brain measures of attention, inhibition and performance-monitoring across a test-battery of three cognitive tasks. **Method:** Using a randomised cross-over design, 29 young men completed three successive cognitive tasks (Cued Continuous Performance Task [CPT-OX]; Eriksen Flanker Task; four-choice reaction-time task [Fast Task]) with simultaneous electroencephalogram (EEG) recording before and after a 20-minute high-intensity cycling exercise and resting control session. Cognitive-performance measures, EEG power and event-related potential measures, were obtained during the tasks. Random-intercept linear models were used to investigate the effects of exercise, compared to rest, on outcomes. **Results:** A single bout of exercise significantly ($p<0.05$) increased the amplitude of the event-related potential Go P3, but had no effect on the contingent negative variation (CNV), Cue P3 or NoGo P3, during the CPT-OX. Delta power, recorded during the CPT-OX, also significantly increased after exercise, whereas there was no effect on cognitive-performance in this task. Exercise did not influence any cognitive-performance or brain measures in the subsequent Flanker or Fast Tasks.

Conclusion: Acute high-intensity exercise improves brain-indices reflecting executive and sustained attention during task performance (Go P3 and delta activity), in the CPT-OX, but not anticipatory attention (Cue P3 and CNV) or response inhibition (NoGo P3) in young-adult men. Exercise had no effect on cognitive-performance or brain measures in the subsequent Flanker and Fast tasks, which may potentially be explained by the time delay after exercise.

6.2 Introduction

Emerging evidence suggests that physical exercise can enhance cognition, brain function and psychological health (Brummer, Schneider, Abel, Vogt, & Struder, 2011; Chang, Labban, Gapin, & Etnier, 2012a; Verburgh, Konigs, Scherder, & Oosterlaan, 2014). Recent meta-analyses, including studies using varying controlled (e.g. randomised controlled, within-subject) and non-controlled (quasi-experimental, observational) methodologies, indicate that even a single bout of aerobic exercise, such as running or cycling, improves neurocognitive function in both children and adults (Chang et al., 2012a; Lambourne, Audiffren, & Tomporowski, 2010; McMorris & Hale, 2012; McMorris, Sproule, Turner, & Hale, 2011; Roig, Nordbrandt, Geertsen, & Nielsen, 2013; Verburgh et al., 2014).

Positive effects, particularly of acute (short-lived) exercise sessions of 20 minutes or more in duration (Chang et al., 2012a), have been reported in experimental studies on a range of cognitive performance measures. These measures include inhibition and interference control (Effect size; ES=0.25-0.46) (Chang et al., 2012a, Verburgh et al., 2014), attention (ES=0.42), mean reaction time (MRT) (ES=0.30-1.41) (McMorris et al., 2011; 2012) and short-term memory (ES=0.26) (Roig et al., 2013). Several studies suggest that effects are largest for executive functioning, such as response inhibition and interference control (Chang et al., 2012a; Kramer & Erickson, 2007; Tomporowski, Davis, Miller, & Naglieri, 2008). However, relatively few studies have investigated effects on measures of attention and attentional lapses (Chang et al., 2012a) and findings on executive functioning and MRT have been mixed, as some studies fail to replicate the beneficial effect of acute exercise (Coles & Tomporowski, 2008; Wang et al., 2015). These inconsistent findings might be explained by differences in the experimental paradigms used, such as the intensity of exercise, fitness level of participants and time lapse after exercise (Chang et al., 2012a), as well as by differences in the tasks and aspect of cognitive functions being studied.

A growing body of research has also incorporated neurophysiological methods, such as electroencephalography (EEG), which provides a direct measurement of brain activity, to better understand the neural processes enhanced by exercise (Chang, 2016; Hillman, Snook, & Jerome, 2003). Experimental studies have reported beneficial effects of acute exercise in children and adults on brain activity relating to attentional and arousal processes. These findings include increased alpha (Brummer et al., 2011; Mierau et al., 2014; Moraes et al., 2011; Schneider, Brummer, Abel, Askew, & Struder, 2009b; St-Louise-Deschenes, Moore, & Ellemberg, 2015a) and beta spectral power (Moraes et al., 2007; 2011; Schneider et al., 2009b), mainly in frontal and parietal areas, during resting-state conditions, which are thought to index background processes such as arousal and activation. However, the direction of these effects on alpha and beta EEG power have been mixed and findings have been inconsistent (Brummer et al., 2011; Mierau et al., 2014; Moraes et al., 2007; Schneider et al., 2009a; St-Louise-Deschenes et al., 2015a). No effect has been found for slower-wave delta and theta activity during resting-state (Moraes et al., 2011; Schneider et al., 2009a). Discrepancies in study findings are likely due to heterogeneity in study methodologies and exercise paradigms (Schneider et al., 2009a; Stroth et al., 2009; St-Louise-Deschenes et al., 2015a), but also a lack of a control group in some studies (Fumoto et al., 2010; Mierau et al., 2014; Schneider et al., 2009a).

Fewer studies have investigated the effect of acute exercise on event-related potentials (ERPs), which are time-locked brain responses to specific events. The most consistent finding has been an exercise-induced increase in P3 amplitude in Flanker and Go/No-go tasks, during target stimulus presentation (Go P3), which reflects attention allocation and execution (Chang, Pesce, Chiang, Kuo, & Fong, 2015a; Hillman et al., 2003; Drollette et al., 2014; Kamijo et al., 2004b; 2007; St-Louise-Deschenes, Moore, & Ellemberg, 2015b). Enhancements in Go P3 amplitude after acute exercise have in some studies been paralleled with improved behavioural performance of faster reaction times (Kamijo et al., 2007; 2009; Ludyga et al., 2017; Wang, Shih, & Tsai, 2016), and increased performance accuracy (Drollette et al., 2014; Hillman, Kamijo, &

Scudder, 2011). Although most acute exercise research has focused on the Go P3 component, a small number of studies have also reported beneficial effects of exercise on the NoGo P3 (inhibition of a response) (Kamijo et al., 2004b), the contingent negative variation (CNV; response preparation) (Stroth et al., 2009; Tsai et al., 2014), and the N2 (conflict monitoring) (Drollette et al., 2014; Stroth et al., 2009). The literature on the effect of exercise on brain measures of specific cognitive processes is still limited and few studies have explored effects across several cognitive tasks and ERP components in a single testing session.

A few studies have explored if aerobic fitness of participants, often measured as the peak oxygen consumption (VO_{2peak}), moderates the beneficial effects of acute exercise on cognitive performance. While some research suggests that individuals with higher fitness levels improve more from acute exercise on a range of cognitive-performance measures (Chu, Chen, Hung, Wang, & Chang, 2015; Chang, Chu, Wang, Song, & Wei, 2015b; Hogan et al., 2013), findings have been mixed and a meta-analysis did not confirm a moderating role of fitness (Chang et al., 2012a). More limited studies have investigated the moderating role of fitness on the effects of exercise on EEG/ERP outcome measures. While one study failed to find moderating effects of fitness on the relationship between acute exercise and alpha event-related desynchronization (Chang et al., 2015b), another study found that only 'unfit' individuals showed higher levels of coherence in the alpha band after rest compared to exercise in NoGo task trials, possibly indicating greater allocation of cognitive resources to the task demands (Hogan et al., 2013). The limited and inconclusive research warrants further investigation of the effect of individual fitness level on the beneficial effects of acute exercise.

6.2.1 Aims

We aimed to investigate the effects of a single bout of high-intensity aerobic cycling exercise on a range of performance and EEG measures implicated in attention, inhibition and performance-monitoring, in a population sample of young adult men. Using a cross-over trial design, outcome measures were obtained during three

successive cognitive conditions, 30 to 64 minutes after cycling exercise or rest, which have been used to identify impairments in several psychiatric and neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) (Cheung et al., 2017; Michelini et al., 2016a; 2016b). The primary aim was to examine the effects of acute exercise across performance and brain measures that are either well- or under-studied in the exercise literature, to better understand the specific cognitive and brain processes that improve from acute exercise. Our secondary aim was to investigate if the degree of improvement from exercise on identified performance and brain measures is related to aerobic fitness and physical activity levels of the participants. This may shed light on characteristics of individuals who would especially benefit from exercise interventions.

6.3 Materials and methods

6.3.1 Participants

We recruited 29 men between the ages of 18 and 26 (mean=21.5; standard deviation [SD]=2.52) years, of whom 22 were graduate/postgraduate students, 4 were employed and 3 were unemployed. We only included men to reduce sample heterogeneity and increase power in our study. Participants were recruited from a recruitment website for research (callforparticipants.com), through posters in the community near the research centre and through internal advertisement at King's College London. Participants had an average IQ of 111.72 (SD=11.33). Exclusion criteria were having any cardiovascular or metabolic disease (e.g. diabetes), being obese (BMI>30), having bone or joint problems, epilepsy, asthma or any other lung disease. None of the participants were on any psychiatric medication which may have had an influence on cognitive performance. In Figure 6.1, we display a CONSORT flow diagram of participants through each stage of the trial for information on participant drop-out (N=3) and the random allocation of participants to the intervention groups. The study was approved by the Research Ethics Committee at King's College London (Ref: HR-15/16-3032) and informed consent was obtained from participants before testing.

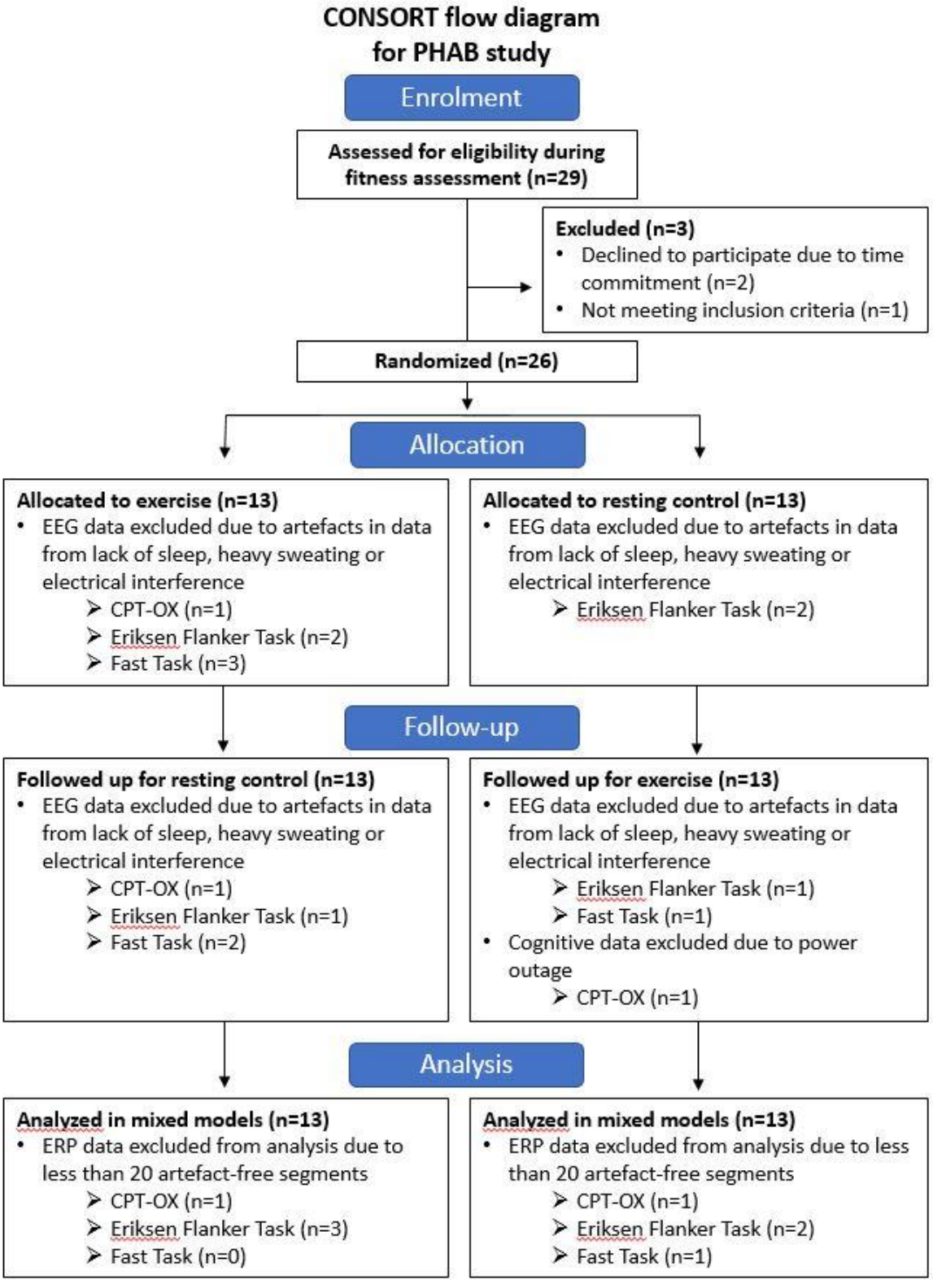


Figure 6.1 CONSORT flow diagram.

6.3.2 Procedure

This cross-over trial comprised of three laboratory visits conducted over a range of 11 to 21 days. The assignment of participants in each trial arm was randomised. Participants attended all three testing sessions at the same time of the day for all three assessments, either in the morning or afternoon.

Visit 1: Fitness assessment

At the first initial visit, which occurred 4 to 14 days (mean=7.4, SD=3.6) before the first experimental testing session, each participant underwent an aerobic fitness assessment and health screening procedure. During this first visit, we measured the participant's stature and body weight to calculate body mass index (BMI=weight(kg)/height(cm)^2) and asked the participant to complete a health questionnaire (Physical Activity Readiness Questionnaire). Each participant then performed a continuous step-incremental exercise test to exhaustion in order to determine their VO_{2peak} and gas exchange threshold (GET). Participants were asked to cycle on a cycle ergometer (Monark 874E) at a constant cadence of 70 revolutions per minute at a starting power output of 70 Watts for 5 minutes. Power output was subsequently increased every minute by 28 Watts until participant exhaustion, which was defined as a drop in cadence below 60 revolutions per minute for five consecutive seconds. Test duration was on average 19.3 minutes (SD=2.1), including a 5-minute warm-up and 5-minute cool-down period. Measures of VO_2, carbon dioxide output (VCO_2), minute ventilation (V_E) and respiratory exchange ratio (RER) were recorded during the exercise test using a breath-by-breath metabolic cart, facemask and turbine (Cortex Metalyzer 3B, Leipzig, Germany). The participant wore a wireless chest strap to monitor heart rate (Polar, Electro, Finland). Perceived exertion was measured every minute during the cycle test using a 6-20 Borg rating of perceived exertion (RPE) scale (Borg, 1982). Peak VO_2 was taken as the highest 10 s average VO_2 achieved during the test and was used as a measure of aerobic fitness level after normalising for body weight (mL*min^{-1}*kg^{-1}). The V-slope method was used to determine the GET, which is a non-invasive estimate of the blood lactate threshold (Barker, Williams, Jones, &

Armstrong, 2011; Beaver, Wasserman, & Whipp, 1986). The resistance equivalent to 20% delta (Δ; difference between GET and VO_{2peak}), which is considered high-intensity exercise, was then calculated and verified by two researchers and used for the subsequent exercise trial. The delta concept was used for the exercise condition rather than a fraction of peak VO_2, as it minimises between participant variation in the physiological response to exercise (Lansley, Dimenna, Bailey, & Jones, 2011). High-intensity exercise was chosen because it has been found to have largest effects on cognitive measures when tested after a delay post-exercise (Chang et al., 2012a).

Visits 2 and 3: Experimental sessions

During each of the two experimental testing sessions, which were seven days apart, individuals first performed the three computerized cognitive tasks, while their EEG brain activity was recorded. The cognitive tasks were followed by one of two conditions: 1) a 30-minute exercise bout consisting of 20-minute of exercise at 20% delta with a 5-minute warm-up and 5-minute cool-down; or 2) a 30-minute resting control session. The order of the two testing sessions, i.e. whether a participant attended the exercise or control session first, was counterbalanced. During the exercise intervention, the participant cycled and simultaneously watched a nature documentary (Ocean Giants on BBC, either episodes 2 or 3). During the resting control session the participant was sat on the cycle ergometer without pedalling, while again watching the nature documentary (order of episodes counterbalanced between sessions), in order to standardise paradigms between the two exercise and control sessions. The amount of water consumed by the participant during the first experimental testing session was recorded and they were encouraged to consume the same amount of water on the second experimental testing session. RPE was recorded at the 5^{th}, 10^{th}, 15^{th} and 20^{th} minute of the exercise and control sessions. Heart rate was measured at the end of the testing session. After both testing sessions, the participant was asked to blow-dry his hair before wearing the EEG cap prior to brain activity measurement. The participant was then asked to perform the same three

computerized cognitive tasks performed in the beginning again while brain activity was recorded, 30 minutes post-intervention to allow for the set-up of the EEG cap.

Although participants and researchers were not blinded to the type of intervention that participants were undergoing on the day of testing, researchers were blinded during the pre-processing stage of EEG data.

6.3.3 Measures

The International Physical Activity Questionnaire (*IPAQ) short version* was administered during visit 1 to measure the participants physical activity status (Craig et al., 2003). IPAQ asks participants about physical activities from the last 7 days. Continuous scores were created to estimate how much time participants spend on (1) vigorous intensity physical activity, (2) moderate intensity physical activity, (3) walking and (4) sitting down. A total score of the full amount of time spent on physical activity was also calculated. IPAQ has acceptable measurement properties of reliability and criterion validity, at least as good as other self-report measures of physical activity (Craig et al., 2003).

CPT-OX (Doehnert et al., 2008; Valko et al., 2009). This CPT includes rare cued Go and NoGo conditions embedded in a vigilance task with frequent distractors to assess attentional and inhibitory processes. The test consists of 400 letters presented for 150 milliseconds with a stimulus onset asynchrony of 1.65 seconds in a pseudo-randomised order. The cue letter O occurred with 20% probability (80 Cue stimuli), signaling a subsequent Go/NoGo stimulus, and induced response preparation. Participants were instructed to press a mouse button as fast as possible every time the cue was followed directly by the letter X [(O-X) target sequence, 50% of times after Cue, 40 Go stimuli] but had to withhold responses to O-not-X sequences (NoGo trials, also 50% of times after Cue, 40 NoGo stimuli). We obtained performance measures of mean reaction time (MRT), reaction time variability (RTV; SD of RT), commission errors (CE) and omission errors (OE). MRT and RTV were calculated across correctly answered Go trials, CE were responses to Cue, NoGo and distractor stimuli or Go stimuli not

following a Cue, and OE were non-responses to Go trials. The CPT-OX took approximately 11 minutes for participants to complete.

The Eriksen Flanker Task was an adaptation of the original Eriksen Flanker paradigm designed to increase cognitive load as used in previous studies (Albrecht et al., 2007; McLoughlin et al., 2009). In each trial, a central black fixation mark was replaced by a target arrow (a black 18-millimeters equilateral triangle). Participants had to indicate whether this arrow pointed toward the left or right by pressing corresponding response buttons with their left or right index fingers. Two flanker arrows identical in shape and size to the target appeared 22 millimeters above and below the center of the target arrow 100 milliseconds prior to each target arrow. Both flankers pointed in either the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150 milliseconds, with a new trial being presented every 1650 milliseconds. Two hundred congruent and 200 incongruent trials were arranged in 10 blocks of 40 trials. Performance measures MRT, RTV and number of errors (left-right errors occurring when participants chose the wrong left or right response) were calculated separately for congruent and incongruent conditions. The Eriksen Flanker Task took approximately 13 minutes to complete.

The Fast Task; Baseline Condition is a slow, unrewarded reaction time task and consists of 55 trials (Andreou et al., 2007), which followed a standard warned four-choice RT paradigm. Four empty circles (warning signals, arranged horizontally) first appeared for 8 seconds, after which one of them (the target) was colored in. Participants were asked to press the response key that corresponded to the target position. Following a response, the stimuli disappeared and a fixed inter-trial interval of 2.5 seconds followed. Speed and accuracy were emphasized equally. If participants did not respond within 10 seconds, the trial terminated. We obtained performance measures of MRT and RTV across correct trials. This version of the Fast Task took approximately 10

minutes to complete.

6.3.4 EEG

6.3.4.1 Recording and Pre-processing

EEG was recorded from 62 channels DC-coupled recording system (extended 10–20 montage), with a 500Hz sampling-rate, impedances kept under 10kΩ and FCz as the reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. The EEG data was analyzed using Brain Vision Analyzer (2.0) (Brain Products, Munich, Germany). After down-sampling the data to 256 Hz, the EEG data was re-referenced to the average of all electrodes and filtered offline with digitally band-pass (0.1 to 30 Hz, 24 dB/oct) Butterworth filters. All trials were also visually inspected for electrical artefacts or obvious movement, and sections of data containing artefacts were removed manually. Ocular artifacts were corrected using Independent Component Analysis (ICA) (Jung et al., 2000). The extracted components were manually inspected and components reflecting ocular artifacts removed by back-projection of all but those components. Sections with other artifacts exceeding ± 100 microvolt (μV) in any channel were automatically rejected. Channels that had been removed due to excessive artefacts were replaced with topographic spline interpolation after ICA, to estimate virtual EEG activity based on artifact-free activity from other channels.

6.3.4.2 ERP analyses

ERP analyses involved standard procedures including EEG data segmentation and averaging. Average ERPs were computed separately for each participant, were free from residual artifacts and contained a minimum of 20 artefact-free segments.

CPT-OX: In the CPT-OX, baseline correction was performed using a 500-milliseconds pre-stimulus reference period in line with our previous study using the same task (Michelini et al., 2016b). Stimulus-locked epochs (stimulus window from -200 to 1650 milliseconds) were averaged based on three different response conditions to Cue, Go

and NoGo stimuli. Average ERPs only included trials with correct responses or correctly rejected trials. ERP components were identified within the selected electrodes and latency windows for which effects were expected to be largest, based on previous studies (Albrecht et al., 2013; Michelini et al., 2016b; McLoughlin et al., 2010; 2011b), and verified against the topographic maps and grand averages (Figures 6.2 and 6.3). In Cue trials, the P3 was measured as the highest peak amplitude at Pz between 250-600 milliseconds and the CNV was measured as the mean amplitude at Cz between 1300-1650 milliseconds. In NoGo trials, the P3 was measured as the highest peak amplitude at Cz between 250-550 milliseconds. In Go trials, the P3 was measured as the highest peak amplitude at Pz between 250-500 milliseconds.

Eriksen Flanker Task: In the Flanker task, baseline correction was applied using -300 to -100 ms pre-target (-200 to 0 milliseconds pre-flanker) interval. Analyses of ERN and Pe components were restricted to incongruent trials, as not enough errors are made during congruent trials in this task to allow reliable measurement of ERPs (i.e. at least >20 segments). Data were segmented based on stimulus-locked congruent and incongruent trials where a correct response was made (N2) and response-locked (error-related) incongruent trials where an incorrect response was made (ERN and Pe). The electrodes and latency windows for ERP analyses were selected based on previous studies (Albrecht et al., 2007; Michelini et al., 2016a; McLoughlin et al., 2009), topographic maps, and the grand averages. The N2 was measured as maximum negative peak at the FCz electrode between 250-450 milliseconds after target onset. The ERN was measured as a difference from the preceding positivity (PNe, -100 to 50 milliseconds) and measured at FCz between 0 to 150 milliseconds. This peak-to-peak measure was chosen over a maximum peak measure as it has proven to be a robust measure of this component (Falkenstein et al., 2001; Geburek, Rist, Gediga, Stroux, & Pedersen, 2013; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). The Pe was measured as maximum positive peak at the CPz electrode between 150 and 450 milliseconds after an erroneous response on incongruent trials.

Fast Task: In the Fast Task, baseline correction was performed using 200-milliseconds pre-stimulus reference period, in line with other studies using this task (Cheung et al., 2017; Michelini et al., 2018). P3 amplitude was analysed as the maximum amplitude at Pz between 250 and 500 milliseconds following the target. The electrode and latency window used were selected based on previous work from our group (Cheung et al., 2017; Michelini et al., 2018), topographic maps and the grand averages.

6.3.4.3 EEG frequency analyses

We estimated absolute EEG power (μV^2) in each task by computing spectral power in the delta (0.5-3.5 Hertz; Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–30 Hz) bands using the Fast Fourier Transform (FFT). In line with previous studies (Rommel et al., 2016; Skirrow et al., 2015), absolute EEG power (μV^2) within each frequency band was averaged across frontal (Fz, F1-F8), central (Cz, C1-C6) and parietal (Pz, P3-P8) regions from individual scalp electrodes to reduce the number of statistical comparisons.

6.3.5 Statistical analyses

We ran 2x2 random-intercept linear models in STATA 14 (StataCorp, College Station, TX) to test the effect of acute exercise on cognitive and EEG measures by examining main and interaction effects of Condition (Exercise and Resting control) and Time (Pre- and Post-intervention). For the EEG frequency analyses, we ran 2x3 random-intercept linear models to test the main and interaction effects of Condition, Time and Region (Frontal, Central, Parietal areas). If significant Time-by-Condition interaction effects emerged, we ran additional contrasts of marginal linear predictions to compare the change in outcome measures before and after exercise (Pre- minus Post-intervention value) between each Condition. We chose to run mixed models instead of repeated measures ANOVAs because they deal with missing data through maximum likelihood and have less strict assumptions on normality of the data, both of which are advantageous when analysing small samples. The outcome measures CE and OE were severely skewed (+/- 2) and were therefore log-transformed (George & Mallery, 2010). Cohen's d effect sizes are presented along with test statistics, to compare group

means, where $d \geq 0.20$ is a small effect, $d \geq 0.50$ is a medium effect and $d \geq 0.80$ is a large effect (Cohen, 1988).

We further ran Spearman's rank correlations of each of the fitness level (VO_{2peak}) and physical activity (IPAQ) measures with difference-scores (Post- minus Pre-exercise intervention) on outcomes that showed significant improvement after exercise. We controlled for the change in outcome after the resting control condition.

6.4 Results

See Table 6.1 for descriptive data of the participants and measures obtained during the initial fitness assessment. Table 6.2 summarises manipulation data obtained during the exercise and resting control sessions.

Table 6.1 Participant characteristics

Measures	Mean (SD)
Body mass index (BMI), kg/cm^2	22.54 (2.86)
Underweight; BMI<18.5 (n=2)	
Normal; BMI=18.5-25 (n=23)	
Overweight; BMI=25-30 (n=4)	
PA levels, MET-minutes/week	3,480 (2,657)
VO_{2peak}, l/min	2.85 (0.69)
VO_{2peak}, $ml*min^{-1}*kg^{-1}$	39 (8)
GET, l/min	1.70 (0.43)
GET, $\%VO_{2max}$	60 (8)
Power output, Watt	262 (56)
HR at end of fitness assessment	183 (13)
RPE at end of fitness assessment	18 (1)

PA levels: Physical activity levels from IPAQ, MET: Metabolic equivalent, VO_{2peak}: maximal oxygen uptake, GET: gas exchange threshold, HR: Heart rate; beats/min, RPE: Borg rating of perceived exertion scale.

Table 6.2 Physiological and perceptual outcomes during testing sessions

Measures	Mean (SD)
Exercise intervention	
% Completion of trials	100
RPE at end of session	19 (1)
HR at end of session, beats/min	180 (11)
Mean VO_2, l/min	1.90 (0.40)
Mean VO_2, $ml*min^{-1}*kg^{-1}$	26 (5)
$\%VO_{2peak}$	68 (10)
Peak VO_2, l/min	2.74 (0.59)
Peak VO_2, $ml*min^{-1}*kg^{-1}$	38 (7)
Power output, Watt	167 (44)
Mean %Δ	21 (26)
Resting control	
% Completion of trials	100
Perceived exertion at end of session	6 (1)
HR at end of session	75 (13)
Mean VO_2, l/min	0.32 (0.06)
Mean VO_2, $ml*min^{-1}*kg^{-1}$	5 (1)
$\%VO_{2peak}$	12 (2)

RPE: Borg rating of perceived exertion scale, VO_{2peak}: maximal oxygen uptake, GET: gas exchange threshold, HR: Heart rate; beats/min, Δ: difference between GET and VO_{2peak}.

6.4.1 CPT-OX

Means and standard deviations of cognitive performance, ERP and EEG frequency measures before and after the exercise and resting control interventions are summarised in Table 6.3 (see Table S1 for EEG frequency band values within each brain region separately).

Two participants had missing EEG data at one visit due to excessive artefacts in the data; one was heavily sweating and the other experienced a lack of sleep. A further participant was excluded from the ERP analysis due to having less than 20 artefact-free segments at both visits. One individual had missing cognitive-performance data during one visit due to technical issues (see Figure 6.1).

Table 6.3 Means and standard deviations of cognitive and brain measures during each Time point (Pre- and Post-intervention) and Condition (Exercise and Resting control) during the CPT-OX.

	Exercise intervention		**Resting control**	
	Pre	**Post**	**Pre**	**Post**
MRT	370.82 (41.08)	370.56 (45.72)	374.55 (60.12)	378.13 (51.91)
RTV	80.03 (42.54)	105.24 (59.37)	83.73 (51.50)	94.76 (59.12)
OE	1.04 (1.48)	2.04 (3.36)	1.92 (3.58)	3.27 (5.74)
CE	1.04 (1.22)	1.84 (1.93)	1.27 (1.99)	2.27 (2.81)
CNV	-2.80 (1.94)	-3.06 (2.97)	-2.35 (2.23)	-2.89 (2.30)
Cue P3	5.25 (2.64)	5.25 (2.82)	4.99 (2.86)	5.02 (2.92)
NoGo P3	7.43 (4.01)	8.43 (5.86)	7.31 (5.51)	8.65 (5.74)
Go P3	8.18 (4.18)	9.34 (5.49)	8.17 (4.51)	8.45 (4.63)
Delta	3.85 (2.60)	5.44 (4.28)	3.97 (2.22)	4.32 (2.20)
Theta	0.53 (0.50)	0.68 (0.64)	0.63 (0.67)	0.73 (0.70)
Alpha	0.83 (1.61)	1.06 (1.71)	0.94 (1.81)	1.11 (1.82)
Beta	0.11 (0.05)	0.15 (0.09)	0.13 (0.07)	0.14 (0.06)

CPT-OX: Cued Continuous Performance Task, MRT: Mean reaction time, RTV: Reaction time variability, OE: Omission error, CE: Commission error, CNV: Contingent negative variation. Average EEG frequency band measures are reported across all brain regions (see Table S1 for each frontal, parietal and central regional measure).

6.4.1.1 Cognitive performance data

The random-intercept models did not reveal any significant Condition-by-Time interaction effects on any of the cognitive measures (all $p>0.05$): OE, CE, MRT or RTV (Table 6.4). We found significant main effects of Time for RTV, CEs and OEs, showing that RTV (from M=81.88 milliseconds [SD=37.48] to M=100.88 milliseconds [SD=49.05]), CEs (from M=1.15 [SD=1.64] to M=2.06 [SD=2.40]) and OEs (from M=1.48 [SD=2.24] to M=2.72 [SD=4.08]) increased over time, on average, across the exercise and resting control conditions. No other main effects were observed for cognitive measures (Table 6.4).

6.4.1.2 ERP data

The random-intercept models revealed a significant ($p=0.03$) Condition-by-Time effect on the Go P3. Post-hoc comparisons revealed that the Go P3 amplitude significantly increased after exercise ($d=0.24$, $p=0.008$) but not after the resting control condition ($d=0.06$, $p=0.61$) (Table 6.4).

We found no other significant interaction effects on the CNV, Cue P3 or NoGo P3 amplitudes and only one significant main effect of Time on the NoGo P3, showing that the amplitude increased from pre- to post-intervention (from M=7.40 µV [SD=4.38] to M=8.63 µV [SD=5.65]), across the exercise and resting control conditions (Table 6.4).

6.4.1.3 EEG frequency data

The random-intercept models revealed no significant Condition-by-Time-by-Region effects on any of the EEG frequency bands, but did reveal a significant Condition-by-Time interaction effect on delta activity, across regions. Post-hoc comparisons showed that delta activity significantly increased after exercise ($d=0.37$, $p<0.001$), but not after the resting control session ($d=0.11$, $p=0.46$) (Table 6.4). No other interaction effects were significant.

The analyses revealed significant ($p<0.05$) main effects of Region across the frequency bands (Table 6.4). The effect of Time was significant for delta (from M=3.60 μV^2

[SD=1.56] to M=4.38 μV^2 [SD=1.91]), theta (from M=0.57 μV^2 [SD=0.59] to M=0.70 μV^2 [SD=0.68]) and beta (from M=0.11 μV^2 [SD=0.04] to M=0.14 μV^2 [SD=0.06]) activity, showing that EEG activity in these bands increased from pre- to post-time points, across exercise and resting control conditions (Tables 6.3 & 6.4). No main effect of Time was found on alpha activity. The effect of Condition was significant only for the theta band, showing that theta activity was higher during the resting control session (M=0.66 μV^2 [SD=0.69]) compared to the exercise session (M=0.59 μV^2 [SD=0.56]), across pre- and post-measures.

To investigate the relationship between the significant increases in delta activity and Go P3 amplitude after exercise, we ran Spearman rank correlations between the change scores (Post- minus Pre-exercise measures). The correlation between change in delta activity and the Go P3 after exercise was not significant (r=0.15, p>0.05).

Table 6.4 Main and interaction effects of Time (Pre- and Post-intervention), Condition (Exercise and Resting control) and Region (Frontal, Central and Parietal) on cognitive and brain measures, during the CPT-OX

		Chi2	*P*-value	Effect size
MRT	NS			
RTV	Time	5.19	0.02	0.34
Omission errors	Time	4.12	0.04	0.28
Commission errors	Time	11.30	<.001	0.48
NoGo P3	Time	4.75	0.03	-0.22
Go P3	ConditionxTime	4.97	0.03	[a]0.24* [b]0.06
CNV	NS			
Delta	ConditionxTime	5.20	0.02	[a]0.37* [b]0.11
	Time	11.09	<.001	0.26
	Region	66.18	<.001	[c]0.77* [d]0.26* [e]0.68*
Theta	Condition	4.16	0.04	0.09
	Time	11.83	0.001	0.18
	Region	83.04	<.001	[c]0.64* [d]0.01 [e]0.53*
Alpha	Region	52.15	<.001	[c]0.24* [d]0.26* [e]0.45*
Beta	Time	9.16	0.003	0.24
	Region	60.26	<.001	[c]0.71* [d]0.19 [e]0.76*

*Presenting significant main and interaction models; p<0.05. Full table in Supplementary Table S2. *p<0.05 for post-hoc comparisons. Post-hoc comparisons: [a]Change after exercise intervention, [b]Change after resting control. [c]Frontal vs Central, [d]Frontal vs Parietal, [e]Central vs Parietal, CPT-OX: Cued Continuous Performance Task, MRT: Mean reaction time, RTV: Reaction time variability, OE: Omission error, CE: Commission error, CNV: Contingent negative variation, NS: Not significant.*

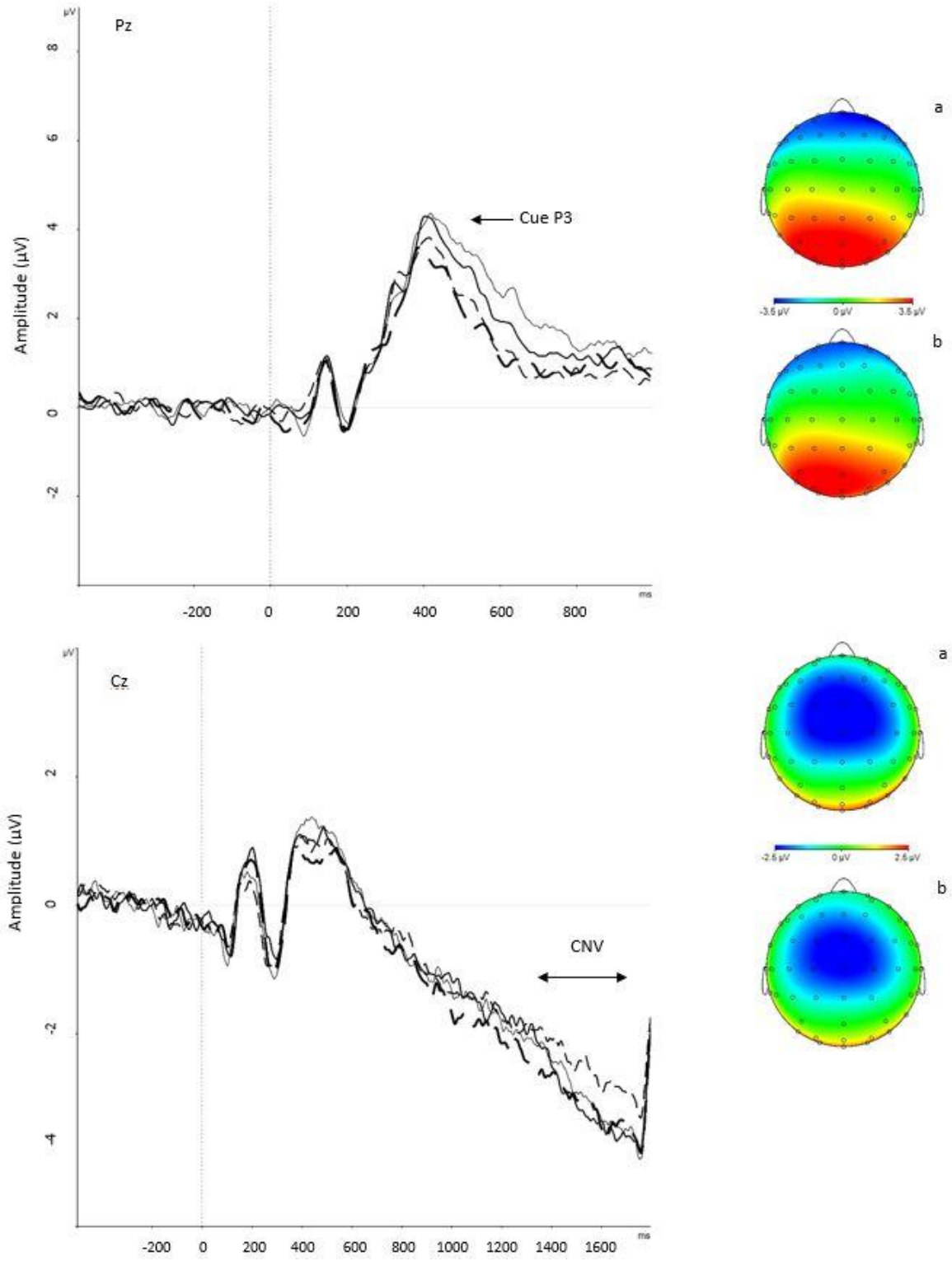


Figure 6.2 Grand average stimulus-locked event-related potentials of the Cue P3 at the Pz electrode (top half) and contingent negative variation (CNV) at the Cz electrode (bottom half) following cue trials, with topographic maps (a) after exercise intervention and (b) after resting control condition.

Thin unbroken line for before exercise intervention, bold unbroken line for after exercise intervention, thin dotted line for before resting control condition and bold dotted line for after resting control condition.

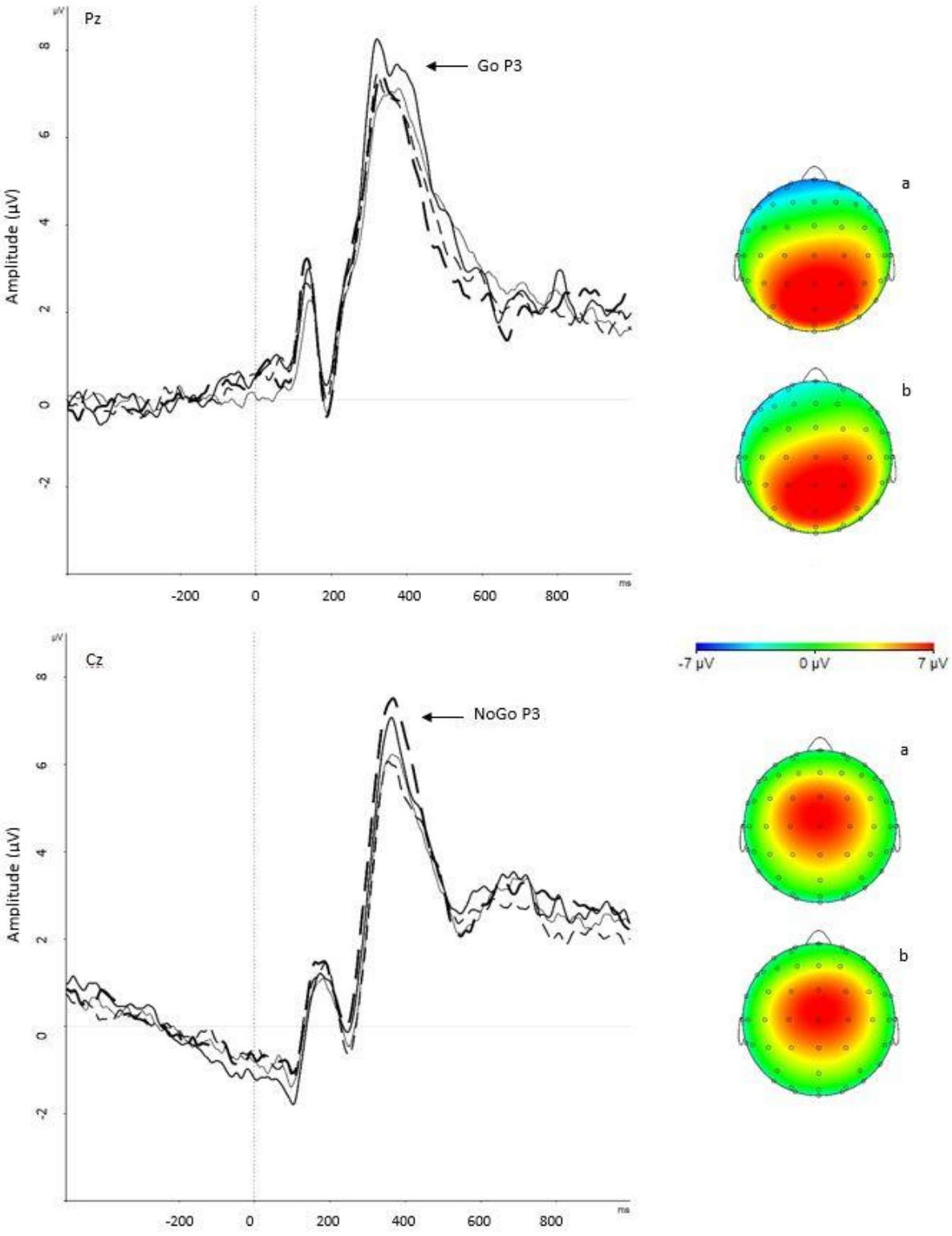


Figure 6.3 Grand average stimulus-locked event-related potentials of the Go P3 at the Pz electrode after the Go stimulus (top half) and NoGo P3 at the Cz electrode after NoGo trials (bottom half), with topographic maps (a) after exercise intervention and (b) after resting control condition.

Thin unbroken line for before exercise intervention, bold unbroken line for after exercise intervention, thin dotted line for before resting control condition and bold dotted line for after resting control condition.

6.4.1.4 Effect of fitness level and physical activity on improvement from exercise

The Spearman's rank correlations did not reveal any significant associations between aerobic fitness level and changes in Go P3 amplitude (r=0.23, p=0.32) or delta activity (r=0.21, p=0.36) after exercise. Physical activity level was not significantly correlated with changes in Go P3 amplitude (r=0.19, p=0.43) or delta activity (r=0.28, p=0.21) after exercise.

6.4.2 Eriksen Flanker Task and Fast Task

Means and standard deviations of cognitive performance, ERP and EEG frequency measures before and after the exercise and resting control interventions are summarised in Tables S3 and S4.

We found no significant Condition-by-Time interaction effects on any of the performance, ERP or EEG frequency band measures in the ERN or Fast Task (Tables S5 & S6).

6.5 Discussion

In this randomised cross-over study of 29 healthy young men, we examined the effect of 20-minutes of high-intensity cycling exercise, compared to resting, on a range of performance and brain measures during three consecutive cognitive tasks (CPT-OX; Eriksen Flanker Task; Fast Task). In the CPT-OX, we found that exercise improved executive attention, indexed by enhanced Go P3 amplitude, but not anticipatory attention (Cue P3 and CNV) or inhibitory processing (NoGo P3). Exercise further enhanced delta power during the task, which may suggest improved sustained attention after exercise (Harmony et al., 1996; Knyazev, 2012; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008). Neither aerobic fitness nor physical activity levels were significantly correlated with the degree of improvement in the Go P3 amplitude or delta activity measures following exercise. We did not find any effects on performance measures or any of the outcome measures during the later Flanker and Fast tasks.

These findings provide insight into the specific processes that may improve following physical aerobic activity.

Our findings suggest that acute high-intensity exercise improves executive attention, indexed by Go P3 amplitude in the Go/NoGo paradigm of the CPT-OX, which relates to increased attention to the task as you respond to the target stimuli. We did not find improvement in ERP components of anticipatory attention or inhibitory processing in the task, contrary to two studies in adults that have found improvements in the CNV during a visuo-spatial attention task (Tsai et al., 2014) and the NoGo P3 during a Go/NoGo task (Kamijo et al., 2004b). The discrepancy in findings may be explained by differences in experimental tasks or study design, such as differences in the time lapses between exercise and cognitive task performances. Previous studies had time lapses of 3 (Kamijo et al., 2004b) and 15-20 (Tsai et al., 2014) minutes, compared to the longer lapse of 30 minutes in our study. While most exercise studies have solely focused on the P3 component in isolation from other ERPs, our study, looking across ERP measures, confirms that the enhanced P3 amplitude following exercise is the most robust ERP finding in the exercise literature (Hillman et al., 2003; Chang et al., 2015a), and may possibly have the longest-lasting effect after exercise.

We also report for the first time that acute high-intensity exercise enhanced slow delta band activity, across parietal, frontal and central brain regions, during cognitive task performance in the CPT-OX. Drawing on the cognitive-neuroscientific literature, this finding may suggest an improvement in sustained attention after exercise, as increased delta activity during task performance has been linked to attentional processes across experimental paradigms (Harmony et al., 1996; Knyazev, 2012; Lakatos et al., 2008). Yet, the improvements in Go P3 amplitude and delta activity were not significantly related, suggesting that these two measures may tap into different aspects of attention. While several previous studies have reported that the P3 component is largely explained by an increased event-related delta response (Prada, Barcelo, Herrmann, & Escera, 2014; Harper, Malone, & Bernat, 2014), less is known about how

delta activity throughout a task relates to the event-related P3 components. Previous exercise studies have investigated EEG bands only during resting-state and reported increases in fast-wave brain activity (reflecting wakeful alertness and cortical activation), often immediately after exercise (Moraes et al., 2007; Schneider et al., 2009b), but not in slow-wave activity (reflecting drowsiness). We now add to the literature by showing beneficial effects in slow-wave delta activity during cognitive engagement, which instead may reflect attentional processing (Harmony et al., 1996; Knyazev, 2012; Lakatos et al., 2008). One implication of our findings is that the identified specific neurophysiological processes that improve from exercise may be modifiable and suitable targets for exercise intervention programs for psychiatric and neurodevelopmental disorders, where these processes are often impaired (Tye et al., 2014; Ertekin, Ucok, Keskin-Ergen, & Devrim-Ukoc, 2017).

While we find that neither aerobic fitness nor physical activity level was associated with how well individuals improved in the Go P3 or delta activity measures, previous research on the interacting effect of aerobic fitness on the beneficial effects of exercise on brain measures has been scarce and inconclusive (Chang et al., 2015b; Hogan et al., 2013). Here we add to the literature by showing that aerobic fitness did not influence the improvement in brain measures of attention, and extend the research by also showing that participants' average level of physical activity did not influence the effect of exercise. One issue to consider, however, is that we may have been under-powered to detect significant correlations of aerobic fitness and physical activity levels with change in outcome measures after exercise. Based on power calculations (using G*Power 3.1) in our sample of 29 participants, we would only be sufficiently powered to detect moderate-to-large effects. Thus, further research is needed using larger samples to determine the role of aerobic fitness and physical activity level on the effects of acute exercise on brain measures.

The beneficial effects of exercise on brain indices of sustained and executive attention were not reflected by behavioural task performance. While some previous studies

have found parallel improvements in processing speed and performance errors with increased Go P3 amplitude (Drollette et al., 2014; Kamijo et al., 2007; 2009), another study has solely found improvements in brain measures, similarly to our current study (Mierau et al., 2014). Possible explanations for the lack of effects on task performance may be that (1) brain measures are more sensitive to the effects of exercise in the CPT-OX, (2) the CPT-OX task may have been too easy, creating ceiling effects (supported by the fact that 52% of the time individuals made no omission errors during task performance), and (3) effect sizes of exercise are lower for performance measures which might result in too little power to detect these as significant in our relatively small sample.

We found no effects of acute high-intensity exercise on any of the measures during the subsequent Flanker or Fast Tasks following the CPT-OX. One possible explanation for the lack of significant findings in these later tasks is the time lapse between the execution of exercise and the performance of the two tasks, leading to wash out of any potential effects of exercise. Participants performed the Flanker and Fast tasks approximately 41 to 54 minutes and 54 to 64 minutes, respectively, after the exercise. This potential interpretation is in line with some previous studies on the effect of acute exercise. An EEG study found that activity in the alpha frequency band was inversely correlated with the amount of time elapsed since exercise cessation (Crabbe & Dishman, 2004) and a meta-analysis reported that the acute effect of exercise on cognition, across tasks, was only significant within the first 15 minutes after exercise (Chang et al., 2012a). Further, in the present study, the increased Go P3 amplitude after exercise in the CPT-OX was not replicated for the target P3 component in the subsequent Fast Task, even though both components reflect attention to target stimuli requiring a response. Another possible explanation for the lack of findings in the Flanker and Fast Tasks may be due to the different nature of the tasks, however, we were unable to investigate this further, as the tasks were not randomly counterbalanced.

One should interpret our findings in light of the study limitations. As we did not counterbalance the order of cognitive tasks, we could not investigate in more detail the influence of time lapse or cognitive load on the effects of exercise, as this was not our primary focus. Further, while we were interested in studying the effects of a 20-minute high-intensity exercise session, we could not separate this effect from that of the total 30-minute exercise including the warm-up and cool-down elements. While this issue is important to note, the warm-up and cool-down elements of the exercise session are standard practice in exercise trials for safety precautions (e.g. avoiding post-exercise syncope). It is also important to note that only males were included in the study, and therefore it would be informative to investigate the generalizability of our findings by replicating analyses in females and examining effects of sex in a large, well-powered sample. Lastly, our sample size was relatively small, although similar in size to the majority of acute exercise studies in the literature (Moraes et al., 2007; 2011; Schneider et al., 2009b; St-Louise-Deschenes et al., 2015a), thus, larger-scale double-blinded experiments are needed to confirm our findings.

6.6 Conclusion

In this randomised cross-over study, we found that 20 minutes of acute high-intensity exercise improved brain measures of executive and attentional processes during a continuous performance task, but not measures of anticipatory attention or inhibitory processing. Exercise had no effect on behavioural performance or brain measures in subsequent Flanker and Fast Tasks, which could be due to time delay or level of cognitive load. Insights on the specific processes that improve from exercise may be used to understand the cognitive-electrophysiological targets for intervention programs for psychiatric and neurodevelopmental disorders.

CHAPTER 7 – Discussion and conclusions

7.1 Abstract

In this concluding chapter, I will provide a summary of the key findings from the five data-based chapters. I will go on to discuss wider implications of these findings on informant source validity and biological correlates of ADHD, relating to both research and clinical contexts. Strengths and limitations of the research will then be highlighted along with future directions.

7.2 Summary of aims

This thesis aimed to investigate informant source validity as well as genetic and neurobiological underpinnings of ADHD in adolescents and adults using a multi-disciplinary approach. In the first part of the thesis, the aim to was to evaluate the validity of informant sources for ADHD by examining associations of informants with cognitive-neurophysiological correlates and future adverse life outcomes using both clinical and epidemiological samples. In the second part of the thesis, the overall aim was to further our understanding of different aspects of biological factors associated with ADHD using both clinical and population samples. Specifically, the aims were to (1) examine the genetic associations between ADHD and commonly co-occurring traits and disorders, (2) establish the stability of autonomic arousal profiles in ADHD, indexed by electrodermal activity, and (3) study the effects of acute physical exercise on cognitive-neurophysiological measures of attention, inhibition and performance-monitoring.

7.3 Key findings

7.3.1 Self-report of ADHD shows limited agreement with objective markers of persistence and remittance

The first study in this thesis (Chapter 2) aimed to investigate how well self-report is reflected by objective (cognitive-neurophysiological and actigraph) measures, which have previously been shown to discriminate between ADHD persisters, remitters and

controls using parent-report (Cheung et al., 2016), in 108 adolescents and young adults with childhood ADHD and 167 controls (the SEFOS sample).

The findings showed that the objective data were better at distinguishing between persistent and remittent groups when these were based on parent-report, compared to self-report. Furthermore, the concordant (meeting ADHD criteria according to both informant reports) and discordant (meeting ADHD criteria according to parent report only) groups significantly differed from controls on most measures and did not differ from each other on any objective measure, suggesting that self-reports of ADHD at follow-up added little value over and above parent-report alone in the association of ADHD with the objective measures studied.

The analyses on continuous measures of ADHD symptoms revealed that self- and parent-reports showed similar patterns of associations with the objective measures, suggesting a quantitative difference between self- and parent-reported symptoms, as they differed in mean severity. Self-reported impairment correlated significantly with fewer objective measures than parent-reported impairment, suggesting a qualitative difference between the informants. This suggests that individuals evaluate their level of impairment based on other factors than their parents.

This is the first study to suggest that self-report of ADHD outcome in adolescents and young adults is not as well reflected by cognitive-neurophysiological and movement data as parent-report. These findings demonstrate that there can be considerable inconsistencies in research findings based on the informant source used, which is important for researchers to acknowledge. For clinicians, the findings also suggest that parent-ratings continue to be important in adolescence and young adulthood and that during the follow-up of children with ADHD, care should be taken to continue to gather reports from multiple informants including parents.

7.3.2 Predictive validity of parent- and self-rated ADHD symptoms in adolescence on adverse socioeconomic and health outcomes

The second study in this thesis (Chapter 3) aimed to compare the predictive associations of ADHD symptoms rated by parents and their children across adolescence on a range of adverse socioeconomic and health outcomes in early adulthood in a population-based sample (TCHAD study; N=2,960).

While past research has shown that ADHD symptoms rated by parents in childhood are associated with adverse life outcomes, the results from this study now showed that both parent- and self-rated symptoms in adolescence were significantly associated with adverse outcomes. Parent-ratings of ADHD symptoms rated in early and late adolescence were (1) more often significantly associated with and (2) generally more strongly associated with the life outcomes compared to self-ratings (ORs=1.12-1.49 versus 1.07-1.17), although the difference between parent- and self-ratings in their predictive strength did not significantly differ for most outcomes. Parent-ratings also predicted several outcomes over and above self-ratings, and the discriminative accuracy did not significantly improve when self-ratings were added to the models compared to when only parent-ratings were used. These findings suggest that despite parent- and self-ratings of ADHD symptoms in adolescence only showing modest correlations (0.36–0.37), self-ratings do not have added value beyond parent-ratings for most life outcomes in young adulthood. While multi-informant approaches (e.g., combining informant source ratings) are commonly used based on the belief that each informant provides unique and valuable information, these results suggest that self-ratings do not provide much information once parent-ratings have been taken into account in predicting most of the outcomes.

The study findings, taken together with the findings in Chapter 2, suggest that parent-ratings have higher predictive and construct validity than self-ratings in adolescence. Thus, even though our findings suggest that self-ratings provide some prognostic information on future life outcomes, the data indicate that obtaining parent-ratings of ADHD symptoms should be the priority in child and adolescent clinical and research

settings. This may change in older adulthood, where parents generally have less frequent contact with their children and therefore have less insight into their children's behaviour and level of functional impairment.

7.3.3 Associations of polygenic risk of attention-deficit/hyperactivity disorder with co-occurring traits and disorders

The third study (Chapter 4) used a powerful polygenic approach, with PRSs derived from the mega-GWAS, to investigate the aetiological overlap between ADHD and frequently co-occurring traits and disorders in a large-scale adult population sample (UK Biobank; N=135,726).

Findings revealed that polygenic load for ADHD predicted higher BMI, risk-taking and neurotic behaviour, depression and anxiety (at a suggestive level), alcohol intake frequency, alcohol dependency, tobacco use and lower general cognitive ability in the general population. These are the first scientific reports of significant genetic associations between ADHD and neuroticism traits, risk-taking, and alcohol use based on genome-wide data. The remaining associations are consistent with a relatively limited literature of studies demonstrating pleiotropy of the genetic variants underlying ADHD (Anttila et al., 2016; Demontis et al., 2018). The overall findings suggest that the co-occurrence of these traits and disorders in ADHD is partly explained by the same common genetic variants. The same pattern of results was found in men and women.

Further research is needed to identify genetic pathways and neurobiological mechanisms relating to these genetic overlaps, which could prove vital for improving prevention and treatment interventions for individuals with ADHD who are at risk for other serious conditions. The common mechanisms underlying ADHD and a co-occurring trait or disorder could either reflect "biological" (or "horizontal") pleiotropy, where similar mechanisms influence both traits, or "mediated" pleiotropy, where certain mechanisms influences one of the traits, which in turn influences the other (Socrates et al., 2017; Solovieff, Cotsapas, Lee, Purcell, & Smoller, 2013).

The study findings also lend further support for the continuous nature of ADHD, with symptoms representing the high end of traits that occur continuously throughout the population. Results showed that common risk alleles that contribute to clinically diagnosed ADHD in children and adults also influenced common traits and disorders in a general population sample of older adults, suggesting that ADHD symptoms represent continuous traits and that similar genetic influences may be present in younger and older individuals. This fits well with the current understanding of ADHD as a continuum of severity based on evidence from behavioural, neurobiological, and genetic studies (Kuntsi et al., 2014; Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Lubke, Hudziak, Derks, van Bijsterveldt, & Boomsma, 2009).

7.3.4 Autonomic arousal profiles in young individuals with ADHD as a function of recording context

The fourth study (Chapter 5) aimed to investigate if autonomic arousal in individuals with ADHD changes over a long testing session and across time, to clarify if arousal profiles are context-dependent or reflect stable impairments, in 71 adolescents and young adults with childhood ADHD and 140 controls (SEFOS).

Findings showed that autonomic arousal profiles of individuals with ADHD varied across testing conditions. ADHD case-control differences in tonic arousal, indexed by SCL, only emerged during a slow and low-demanding cognitive task and differences in phasic arousal, indexed by non-specific fluctuations (NSFs), emerged towards the end of the assessments. Firstly, these findings suggest that lower arousal levels in individuals with ADHD may be especially salient during slow and low-demanding tasks compared to faster-paced and more demanding tasks such as the CPT or the fast-incentive condition of the Fast Task (as demonstrated in James et al., 2016). Our findings further suggest that arousal variability in ADHD may become especially salient over time, possibly in combination with the low-demanding task. Overall, the finding suggests that individuals with ADHD may experience difficulties in regulating their arousal levels rather than experience constant hypo-arousal, which implies that

arousal is malleable in individuals with ADHD and may therefore be suitable as a potential treatment target. The study findings further suggest that inconsistencies in the literature (Hermens et al., 2004; Mayer et al., 2016) may be explained by the different experimental paradigms used across studies.

Analyses further revealed that lower and more fluctuating arousal was associated with a higher level of inattentive and hyperactive-impulsive symptoms, supporting initial findings from a study only in girls (Dupuy et al., 2014). These findings were not accounted for by ODD/CD symptoms, which is in line with previous limited research (Beauchaine et al., 2001; Van Lang et al., 2007). This study using the SEFOS sample is the first larger study to investigate the specificity of both tonic and phasic arousal profiles in young adults with ADHD by controlling for ODD/CD symptoms in analyses. On the other hand, controlling for ODD/CD symptoms enhanced the relationship between phasic arousal and ADHD over time, but it is not clear from these results how ODD/CD symptoms relate to the other variables, as they did not account for the linear associations between NSFs and ADHD symptom domains and were not significantly associated with NSFs. While previous research has suggested that individuals with antisocial/conduct problems have smaller amplitude of specific SCRs (Delamater & Lahey, 1983), less is known of non-specific fluctuations. Further studies are needed to clarify the complex relationship between ODD/CD, NSFs and ADHD, to determine the specificity of fluctuating arousal profiles in ADHD.

Overall, these findings suggest that individuals with ADHD experience difficulties regulating their arousal rather than being constantly under-aroused. Inconsistent findings in the literature on autonomic arousal in ADHD might be explained by differences in experimental designs and tasks.

7.3.5 Beneficial effects of acute high-intensity exercise on electrophysiological measures of attention processes

The final study (Chapter 6) used a randomised cross-over design to investigate the effects of 20-minute high-intensity exercise, compared to resting, on cognitive-

performance and brain measures of attention, inhibition and performance-monitoring, across three consecutive cognitive tasks (CPT-OX; Eriksen Flanker Task; Fast Task), in 29 healthy young men (PHAB).

The findings showed that high-intensity exercise improved executive attention, indexed by Go P3 amplitude in the Go/NoGo paradigm of the CPT-OX, which relates to increased attention to the task as you respond to the target stimuli. Exercise did not influence ERP measures of anticipatory attention or inhibitory processing in the task. While most exercise studies have solely focused on the P3 component in isolation from other ERPs, this study, looking across ERP measures, confirmed that the enhanced P3 amplitude following exercise is the most robust ERP finding in the exercise literature. This study also found, for the first time, that high-intensity exercise enhanced slow delta band activity during cognitive task performance in the CPT-OX. Drawing on the cognitive-neuroscientific literature, this suggests an improvement in sustained attention after exercise. Yet, the improvements in Go P3 amplitude and delta activity were not significantly related, suggesting that these two measures may tap into different aspects of attention. Acute exercise did not influence any of the measures during the subsequent cognitive tasks (Flanker and Fast tasks). It is possible that the greater time lapse between the execution of exercise and performance of these tasks lead to wash out of any potential effects of exercise.

Overall, these findings suggest that brain indices of executive and sustained attention may be modifiable and suitable targets for exercise intervention programs for individuals with attentional difficulties, such as in ADHD. The findings also add to the literature by showing that aerobic fitness and physical activity level did not influence the improvement in brain measures of attention. However, the analyses may have been under-powered to detect significant correlations of aerobic fitness and physical activity levels with change in outcome measures after exercise, based on power calculations (using G*Power 3.1). Thus, further research is needed using larger samples to determine the role of aerobic fitness and physical activity level on the effects of

acute exercise on brain measures, to establish characteristics of individuals who would benefit the most from exercise interventions.

7.4 Wider implications

7.4.1 Validity of parent- and self-report of ADHD in adolescents and young adults

The findings in Chapters 2 and 3 provide convergent evidence that parent-report of ADHD in adolescence and young adulthood has higher validity than self-report, in terms of construct and predictive value, and that self-report may not add additional value over and above parent-report. These conclusions are in line with existing, although limited, literature (Barkley, Fischer, Smallish, & Fletcher, 2002; Brikell et al., 2015) and have direct implications for both research and clinical practice.

Firstly, these findings have important implications for research, in terms of how to diagnose and define ADHD accurately, as the use of different informant sources may explain inconsistencies in ADHD research across studies of adolescents and young adults. For example, recent publications have reported very low ADHD persistence rates in adults (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015) using self-reports, in contrast to studies using self- and parent-report (Biederman et al., 2010; Faraone et al., 2006). Results from Chapter 2 confirm the trend for adolescents and young adults diagnosed with ADHD to show a tendency to report their ADHD symptoms as less severe than their parents (Guelzow et al., 2017; Pierrehumbert et al., 2006), while the opposite pattern is found in population-based samples, where self-ratings are higher than parent- or other-ratings (Merwood et al., 2013; Sibley et al., 2012), as seen in Chapter 3. This may contribute to inflation in reports of adult-onset prevalence in population samples (Agnew-Blais et al., 2016; Moffitt et al., 2015). Further inconsistent results were found in the first part of this thesis (Chapters 2 and 3) where the use of self- and parent-report of ADHD resulted in different findings in regards to associations with cognitive-neurophysiological and movement measures and future life outcomes. While multi-informant approaches (e.g., combining informant source ratings) are commonly used based on the belief that each informant

provides unique and useful information, the results from these two studies suggest that self-ratings in adolescents and young adults do not necessarily provide added valuable insights once parent-ratings have been taken into account. Overall, it should be acknowledged that inconsistencies in the ADHD literature may be explained by the different informant sources used in research. Based on the findings in this thesis, future research studies are encouraged to not rely solely on self-reports of ADHD in adolescent and young adult age groups.

For clinical settings, these findings suggest that parent-report of symptoms and impairment should especially be prioritized in this age group when establishing an ADHD diagnosis, to provide an accurate and valuable diagnosis that captures underlying neurobiological impairments and has prognostic value for future outcomes. Further research is needed to establish if self-report shows increased validity, relative to parent-report or other informant-report (such as spouse/partner), in later ages in adulthood and to establish if any specific aspects of self-report may be more valuable and have more insight than other informants.

7.4.2 Genetic overlap between ADHD and co-occurring disorders

While individuals with ADHD often present with other impairing conditions, little is still known of the specific causes for these co-occurrences. Polygenic analyses in Chapter 4 reported genetic associations between ADHD and several traits and disorders, suggesting that the co-occurrences of other conditions in ADHD, such as lower general cognitive ability, higher BMI, risk-taking and neurotic behaviour, depression and anxiety, alcohol intake frequency, alcohol dependency and smoking may at least in part be explained by overlapping genetic bases. These results are consistent with other lines of research using other quantitative and statistical genetic methods (e.g. Cole et al. 2009; Michelini et al. 2015; Demontis et al. 2018) in suggesting that common biological mechanisms are at play between ADHD and co-occurring conditions. The findings may guide further research into the specific genetic pathways and neurobiological mechanisms that may be useful for clinical applications, by identifying

targets for treatment and prevention of the development of impairing conditions in ADHD.

The identified genetic associations In Chapter 4 may reflect “horizontal pleiotropy”, where the same causal variants contribute to both traits independently, or “mediated pleiotropy”, where the genetic variants affect one of the traits directly (e.g. ADHD) and that trait subsequently influences the other (e.g. high BMI) (Socrates et al., 2017; Solovieff et al., 2013). Future research is needed to establish which type of pleiotropy underlies the identified genetic associations between ADHD and co-occurring traits and disorders. For example, structural equation modelling and related approaches can incorporate genome-wide significant genetic variants or PRS on the traits and disorders to provide insights into the causal relationships between them (Pingault et al., 2018).

7.4.3 Malleability of physiological and neurobiological impairments in ADHD

Findings in Chapters 5 and 6 demonstrate the malleable nature of several physiological and neurocognitive impairments often seen in ADHD from different scientific angles. Existing, although limited, evidence in the ADHD literature suggests that both fluctuations in response speed in cognitive tasks, indexed by high RTV, and low tonic physiological arousal, indexed by SCL, are implicated in ADHD and may be modifiable (James, Cheung, Rijsdijk, Asherson, & Kuntsi, 2016; Kuntsi et al., 2013). This has been evidenced by improvements in these measures during fast-paced, rewarded task conditions (James et al., 2016; Kuntsi et al., 2013). Recent findings, using the same task paradigm (the Fast Task), have additionally demonstrated that the ERP P3, reflecting executive attention, may also be malleable in ADHD, as P3 amplitudes were attenuated only in the slow, unrewarded task condition and normalised in the fast-paced, rewarded condition (Cheung et al., 2017). The results in this thesis now extend these findings by showing that tonic (SCL) and phasic (NSFs) autonomic arousal dysregulation in individuals with ADHD may be context-dependent rather than reflect stable deficits in ADHD. Thus, the autonomic arousal measures may be suitable targets in future non-pharmacological interventions for reaching an optimal state of arousal

and alertness in individuals with ADHD. Further research in this thesis has also reported, using a sample of healthy young adults, that brain indices of executive (P3 amplitude) and sustained (delta activity during task performance) attention may improve from acute exercise. Similarly, these neurocognitive findings suggest that brain indices of executive and sustained attention are modifiable and could therefore potentially be suitable targets for interventions for individuals with attention problems. Taken together, the findings also emphasise the benefits of using fast-paced activities and incentives in learning environments for individuals with attention difficulties (Cheung et al., 2017) and promoting exercise to enhance the regulation of attention and arousal.

7.5 Strengths and limitations

7.5.1 Multidisciplinary approach

This thesis used a multidisciplinary approach to study ADHD in adolescents and adults to attempt to answer research questions from different angles, and taking advantage of the different strengths and limitations of each method used. For example, while clinical samples tend to be smaller in size, due to constraints with participant recruitment and diagnostic procedures, these often have rich study measures with detailed information on participants. Epidemiological samples, on the other hand, may not have as detailed study measures and these are often collected routinely, however, they allow for large sample sizes that increase statistical power. Registered-based data are specifically advantageous due to the objectiveness of measures rather than relying on subjective ratings from participants or their informants. While a multidisciplinary approach is useful for combining different techniques that tackle research questions slightly differently, the approach may also lead to difficulties in bringing together these disparate techniques to form a cohesive conclusion. This thesis has attempted to unify these different techniques and methods by having common threads run through the data-based chapters.

Chapter 2 used a clinical sample to investigate the validity of self-report of ADHD, allowing for association testing between rigorously collected self-reported ADHD measures and detailed cognitive, EEG and movement measures. This methodology informed the design of the study in Chapter 3, which used a larger-scaled population sample with registry data to examine the validity of self- and parent-reported ADHD symptoms. The study in Chapter 3 did not have as detailed ADHD symptom and impairment data on participants, but instead was advantageous in its larger sample size and use of objectively collected life outcome measures. The findings of self-report showing limited validity in comparison to parent-report in Chapters 2 and 3, informed the decision to use parent-reported ADHD in the analyses in Chapter 5. ODD/CD symptoms in Chapter 5 were obtained through self-report, however, this was due to the lack of available parent-reports. The successful use of cognitive-EEG and autonomic arousal measures in Chapters 2 and 5 to discriminate between ADHD and control groups led to the decision to use these measures in Chapter 6, where the effects of exercise were tested on ADHD-related measures in a healthy population sample. Unfortunately, autonomic arousal measures could not be used in Chapter 6 due to technical difficulties with the skin conductance recordings. While I learned that it would have been advantageous to counterbalance the order of cognitive tasks in Chapter 5 to better answer the research question, this unfortunately did not inform the study design in Chapter 6 as the data had already been collected by that time.

Finally, general themes that ran through this thesis were investigations of changes in clinical presentations and aetiology across development and modifiability in ADHD. Chapters 2 and 3 studied the validity of self- and parent-report of ADHD in the transitional stages between childhood and adulthood. While parent- and teacher-report are used as informant sources for ADHD in childhood, these chapters found that parent-report, compared to self-report, showed higher validity also across adolescence and young adulthood. Chapter 4 further showed that genetic variants that contributed to ADHD in children and adults also increased risk for co-occurring traits and disorders

in older adults. The modulation of ADHD-related cognitive-EEG and autonomic arousal measures were also examined by testing how measures were related to persistence and remittance of ADHD (Chapter 2), were modified across recording contexts and time (Chapter 5) and were modified from high-intensity exercise (Chapter 6).

7.5.2 Sample sizes

One of the main strengths to highlight in this thesis is the use of large sample sizes in Chapters 2, 3, 4 and 5 that provided sufficient power to answer important research questions on ADHD. The SEFOS sample used in Chapters 2 and 5 consists of 110 individuals with childhood ADHD and 169 controls. This represents one of the largest follow-up studies of clinical ADHD with available cognitive-electrophysiological measures. The TCHAD sample used in Chapter 3 consists of 1,480 twin pairs with both ADHD symptom rating data and outcome data derived from Swedish national registers, making it a rich and well-powered dataset for the analyses. One exception was for the outcome measure suicide attempt where only 35 (3%) individuals were identified as having attempted suicide. Despite the low prevalence of suicide attempts in the sample, (1) analyses were still able to detect significant associations between ADHD symptoms (parent- and self-rated) and the outcome and (2) the overall conclusions on the comparison of informant sources would not have been affected as the prevalence of the outcome was equally low for analyses using self- and parent-ratings.

The UK Biobank resource used in Chapter 4 is especially large, with a sample of over 150,000 (which has more recently expanded to >500,000) individuals with detailed phenotypic and genotypic data and enabled a large-scale investigation of PRSs, derived from the largest GWAS on ADHD, with co-occurring traits and disorders for the first time. PRSs, however, explained only a small fraction of the variance in the target phenotypes, and to obtain a complete picture of the aetiological overlap between ADHD and co-occurring features will require even larger sample sizes. Further, the analyses were still likely insufficiently powered to detect effects between PRS for ADHD and schizophrenia.

The PHAB study used in Chapter 6 consisted of a sample of modest size with its 29 participants, although participants were assessed twice using a cross-over design to increase power in the analyses. PHAB was originally designed as a pilot study to inform future larger-scale investigations of acute exercise in clinical groups. Even though the PHAB sample was similar in size to a large proportion of studies in the acute exercise literature and the sample was large enough to detect significant effects of moderate-to-large size, the analyses were not powered enough to pick up effects of smaller size. Thus, future larger-scale studies are needed to investigate subtler effects of acute exercise and possible moderating factors.

7.5.3 Dimensional and categorical definitions of ADHD

I employed both dimensional (symptoms and impairment ratings) and categorical (diagnostic cut-off) definitions of ADHD in this thesis. A strength in Chapters 2 and 5 was that both types of definitions could be employed to tackle the research questions. Specifically, in Chapter 2, parent- and self-report were compared in their strength of association with objective measures by comparing both continuous ADHD symptoms and impairments, as well as diagnostic groups of ADHD persisters and remitters. In Chapter 5, the relationship between ADHD and electrodermal measures was examined with both continuous approaches, using ADHD symptoms, and diagnostic approaches, using ADHD case and control groups. Adopting both approaches is valuable to obtain a complete and accurate picture of ADHD, as defining ADHD outcome is a complex issue that different studies have addressed in different ways. While the categorical approach reflects the clinical diagnostic groupings of affected and unaffected individuals, which is needed for treatment decisions, the dimensional approach uses ratings of symptoms and impairments without relying on arbitrary thresholds, better reflecting the research on the continuous nature of ADHD (Kuntsi et al., 2014; Larsson et al., 2012; Lubke et al., 2009). A dimensional approach is beneficial also as it allows investigations of (1) ADHD symptoms and impairments separately, and (2) ADHD using large available population-based samples (such as in Chapters 3, 4 and 6). Findings in this thesis further support ADHD as the extreme of a continuum of traits, as similar patterns of results were obtained using categorical and dimensional approaches to ADHD

(Chapters 2, 3 and 5) and genetic variants underlying clinically diagnosed ADHD were also found to contribute to common traits in the population (Chapter 4).

7.5.4 Generalisability

It should be acknowledged that, because the studies in Chapters 3, 4 and 6 used population-based samples, findings may not generalise to individuals with clinically diagnosed ADHD. Although behavioural, clinical and aetiological research converge in suggesting that ADHD symptoms are the extreme of a normal continuum of behavior in the population (Kuntsi et al., 2014; Larsson et al., 2012; Lubke et al., 2009), it would be informative to examine (1) the predictive validity of parent- and self-ratings, (2) genetic associations between ADHD and co-occurring conditions and (3) the effects of acute high-intensity exercise on cognitive-electrophysiological indices of attention, inhibition and performance-monitoring in clinical samples as well to validate findings.

Furthermore, the age groups of the studies included in this thesis were restricted to adolescents (Chapters 2, 3 and 5) and adults (Chapters 2, 4, 5 and 6). Results may therefore not generalise to other age groups than those studied, especially for cognitive-EEG indices in ADHD, where maturational effects have been well-studied (Liechti et al., 2013; Valko et al., 2009). In studies where age spanned across adolescence and young adulthood (Chapters 2 and 5) and across mid-to-older adulthood (Chapter 4), analyses were run controlling for age to account for any effects due to age. The remaining studies used relatively narrow age groups.

Most participants were males in the SEFOS sample (used in Chapters 2 and 5) and all participants were males in the PHAB sample (used in Chapter 6). The study findings using these samples therefore provide limited information regarding females. It would be informative to investigate the generalisability of our findings by replicating analyses in females and examining sex effects in large, well-powered samples that allow for such comparisons. The TCHAD and UK Biobank samples used in Chapters 3 and 6 have more equal proportions of females and males and therefore the study findings are

more generalisable across sex. Further, the studies using these two samples found that the pattern of results were similar across males and females.

7.5.5 Multiple testing

For several analyses in this thesis (Chapters 2, 5 and 6), multiple testing corrections were not applied because of the exploratory nature of the cognitive, electrophysiological and electrodermal investigations and to limit the type-two error rates (false negative findings). In the three studies involving the SEFOS and PHAB samples, analyses were restricted to measures that were expected to be sensitive to impairments in ADHD and related behaviours. For example, ERP analyses were limited to amplitude measures and not latency measures, as most previous studies using the cognitive tasks have reported alterations mainly in amplitude differences (Cheung et al., 2017; McLoughlin et al., 2009, 2010). Further, the PHAB study was primarily set up as an exploratory pilot-study to inform cognitive-electrophysiological targets in larger-scale exercise trials and therefore I aimed to reduce the chance for false negatives by not applying multiple testing corrections. Due to the exploratory nature of these analyses, future replication of the results is important to validate findings before drawing on conclusions and applying implications of findings in practice. In the interpretation of the study results in these chapters, the emphasis has been placed on both effect sizes and p-values of significance to provide a complete picture of the full impact of the results.

In Chapters 2 and 3, the main study aims were to compare the overall pattern of associations observed for self- versus parent-report of ADHD with objective measures and life outcomes. Multiple testing for the different dependent measures was therefore not applied as these were not relevant to the main research questions comparing self- and parent-report. In the polygenic analyses in Chapter 4, Bonferroni corrections were applied to analyses (Supplementary methods in Appendix B) due to the high-resolution analysis approach, which involved a much higher number of comparisons than in the other studies.

7.5.6 Counterbalancing

The study designs in the SEFOS and PHAB studies entailed participants performing a series of cognitive tasks in a fixed order. As the presentation order of tasks was not counterbalanced, this limited the specific research questions that could be investigated. In the study of electrodermal ADHD case-control differences across resting-state and performance tasks (Chapter 5), I was unable to examine the separate effects of time lapse (i.e. fatigue) and cognitive demand – both which could be explanations for the different physiological profiles of ADHD observed during the different conditions. This was also an issue in the study on the effects of acute exercise on performance across three cognitive tasks (Chapter 6), which limited the conclusions that could be drawn about the specific effects of exercise on cognitive-neurophysiological processes. Future studies that wish to examine measures across different recording tasks should counterbalance the order of tasks to optimise the research questions to be explored.

7.6 Future directions

7.6.1 Replication

Replication of research findings in independent samples using convergent approaches will be required to validate the results in this thesis, as these were for the most part novel. The comparison studies in Chapter 2 and 3 were the first to contrast the predictive and construct validity of self- and parent-report of ADHD in their associations with objective (cognitive, EEG and movement) measures and future outcomes. It would therefore be informative to replicate these analyses to see if they hold using other research samples and investigating other objective measures of ADHD and serious life outcomes. In Chapter 4, several of the reported genetic associations between ADHD and co-occurring conditions confirmed previous limited findings in the genetic literature, while others represented novel associations. Results should therefore be replicated in an independent sample, ideally using an even larger number of participants in regards to the non-significant genetic associations reported for ADHD with BD and schizophrenia, possibly due to low statistical power. As the findings in

Chapter 5 on electrodermal activity in ADHD across recording contexts are completely novel, these will also need to be replicated before firm conclusions can be drawn based on the findings.

It will be especially important to replicate findings from the exercise study in larger samples with sufficient power, as the PHAB study was a relatively small sample compared to the other studies in this thesis. Although the sample was of a small-to-moderate size, the study unravelled informative findings on the beneficial effects of acute exercise on brain indices for executive and sustained attention as indexed by delta power during task performance. However, these analyses were likely not powerful enough to detect small-to-modest sizes, and therefore, future larger studies, ideally including both men and women, will be needed to confirm and generalise these findings.

7.6.2 Informant source validity in older adulthood

The studies described in Chapters 2 and 3 set out to investigate the validity of self- and parent-report of ADHD in adolescents and young adults, and future studies should attempt to extend these analyses to older adults. The research findings in this thesis found relatively low agreement between parent- and self-report of ADHD in adolescents and young adults and further suggested that parent-report has higher validity than self-report and should be prioritised in studies and diagnostic procedures. It would be valuable to extend these findings by exploring the validity of informant sources in older individuals, to identify if there is a certain age where self-report becomes more valuable than other informants. In older adults, informant sources for ADHD in research and diagnosis are often partners/spouses rather than parents, as parents are not always available and may lack insight into their adult children's behaviour as they become more independent. There is currently little research that has compared self- and other-informant sources in middle or late adulthood. One study of individuals aged between 17 and 77 years who were relatives to ADHD probands, reported that both self- and other informant-report (spouses, parents or siblings) ratings scales could predict clinical diagnosis with high accuracy, although the

sample size was small with only ten individuals having an ADHD diagnosis (Magnússon et al., 2006). For future research, it would especially be informative to conduct longitudinal studies, with ADHD ratings collected at multiple time points, to investigate if individuals become more accurate in their own descriptions of experienced ADHD symptomology from younger to older adulthood. It would for example be useful to examine whether the predictive and construct value of self-ratings of ADHD increases at a specific point in development (e.g. middle adulthood). This could be of great value for both clinicians and researchers when having to decide at which age self-report should be used as the main reporting source of ADHD symptoms.

7.6.3 The role of electrodermal activity in the pathway to behavioural impairments in ADHD

Findings in Chapter 5 along with numerous studies in the literature have demonstrated that abnormal physiological arousal profiles, indexed by electrodermal activity, are implicated in ADHD (Barry et al., 2012; Beauchaine et al., 2001; Dupuy et al., 2014). Little is, however, known about the mechanisms and pathways involved in the associations between physiological arousal and ADHD symptomology. A recent study by James et al. (2016) found that attentional lapses during a RT task, indexed by RTV, were associated with lower SCL-indexed arousal. The study further showed that attentional lapses partially explained the pathway between SCL-indexed arousal and ADHD, but there were also direct effects between arousal and ADHD that were not explained by attentional lapses (James et al., 2016). It would be informative to further explore the pathways between physiological arousal and ADHD symptomology by for example (1) replicating analyses by James et al. (2016) using NSF-indexed arousal measures, and (2) investigating additional potential cognitive processes that may be implicated in the pathways. With a greater understanding of the underlying arousal profiles in ADHD and how they are implicated in ADHD symptomology and related cognitive processes, we would be at an advantage for finding appropriate targets for ADHD treatments and interventions.

7.6.4 Large-scale exercise trials

There is a need for large-scale, methodologically strong studies to establish the beneficial effects of physical exercise for individuals with ADHD. Effects of both acute and chronic exercise on ADHD should be investigated using adequately powered, blind sham-controlled randomized clinical trials, ideally establishing both short-term and long-term effects.

Findings in Chapter 6 suggest that acute high-intensity exercise improve brain-indices of executive and sustained attention. These analyses should ideally be replicated in a sample of young individuals with ADHD diagnoses using the same cognitive-neurophysiological test battery, to explore if effects are similar in individuals with greater cognitive-neurophysiological impairment. Ultimately, to inform and optimize exercise interventions in ADHD, studies will need to establish the intensity, frequency and duration of physical activity required to yield benefits for individuals with ADHD, and further explore whether certain individuals benefit more from exercise than others, in terms of factors such as age, fitness levels and levels of function impairments, with sufficient statistical power. Drawing on the findings from the previous data-based chapters in this thesis, it would further be useful to investigate change in ADHD symptoms, based on parent-report, in young individuals with ADHD after high-intensity exercise to establish the beneficial effects on core symptoms. In addition, it would be useful to examine potential pathways of the effect of exercise on ADHD symptoms by examining autonomic arousal and cognitive-EEG recordings simultaneously, as well as any genetic variants that moderate the beneficial effects of exercise.

7.7 General conclusions

Overall, this thesis used a multidisciplinary approach, combining behavioural, neurocognitive, electrodermal and genetic methods, to provide insights into (1) the validity of source-informants used in research and clinical settings, as well as (2) the nature of neurobiological and genetic profiles of adolescents and adult with ADHD and

potential benefits of physical exercise. In the first part of the thesis, findings suggested that both parent- and self-report of ADHD in adolescence and young adulthood may provide some valuable insight into symptoms and impairments, but parent-reports may have higher construct and predictive validity in this age range. In the second part of the thesis, genetic analyses showed that ADHD risk alleles considered 'en masse', using polygenic risk scores, predicted several frequently co-occurring traits and disorders. These findings suggest that common genetic variation underlying risk for ADHD also contributes to higher body mass index, neuroticism, anxiety and depressive disorders, substance use, risk-taking and lower general cognitive ability in the general population. Further, analyses using electrodermal data suggest that abnormal autonomic arousal in ADHD, indexed by electrodermal activity, varies as a function of recording context rather than reflecting stable impairments in the disorder. Finally, results from a randomised cross-over trial show that electroencephalogram (EEG) brain measures of specific and general aspects of attention improved after a single session of high-intensity exercise, suggesting that high-intensity exercise interventions may be appropriate for improving inattentiveness.

In this final chapter, the study findings and implications were discussed along with the strengths and limitations of the research designs, samples and analyses used. Employing a combination of different methodological approaches and levels of analysis, including genetic factors, physiological and neural mechanisms, cognitive processes and behavioural symptoms, is beneficial to provide a complete picture of the pathways and implicated mechanisms in ADHD. Future studies will need to replicate the research findings in this thesis in independent samples to validate novel results.

7.7.1 Overall clinical and aetiological implications

Clinical implications of the findings in Chapters 2 and 3 are that parent-report should generally be prioritised over self-report in adolescents and young adults with ADHD during diagnostic procedures, as parent-report may have higher predictive and construct validity. Clinicians may not always have access to other informants, such as

parents, in young adults with ADHD, however our findings suggest that it is important for clinicians to acknowledge that solely relying on self-reports may have its limitations and that corroborating with other sources of information would be ideal.

Chapter 4 found that polygenic load for ADHD predicted higher BMI, risk-taking and neurotic behaviour, depression and anxiety, alcohol intake frequency and dependency, tobacco use and lower general cognitive ability in the population. These findings reveal that co-occurrences of other traits and disorders in ADHD are largely due to overlapping common genetic variants and that similar genetic influences underlying ADHD are at play across age groups. Aetiological implications of Chapters 5 and 6 are that the findings suggest that abnormal autonomic arousal and neurophysiological indices of ADHD may be modifiable and may not reflect stable impairments. These insights have potential clinical implications in that these neurobiological correlates of ADHD may be suitable targets for treatment of ADHD symptoms and impairment and should be further studied in randomised controlled clinical trials.

7.7.2 Overall conclusions

This thesis found that different methodologies converged in suggesting that parent-report has higher validity than self-report of ADHD in adolescents and young adults. This thesis also provided insights into shared genetic overlaps between ADHD and co-occurring traits and disorders, as well as the modifiability of neurobiological correlates of ADHD.

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Appendix A – Supplementary material for Chapter 3

Table S1.A Predictive value of parent- and self-rated attention-deficit/hyperactivity disorder symptoms across adolescence on academic, occupational and adverse health outcomes; excluding cases with missing values on *either* parent- or self-ratings

	Parent-ratings OR (95% CI)	Self-ratings OR (95% CI)
	Crude	Crude
13-14 years		
No graduate degree	1.20 (1.11, 1.30)**	1.07 (1.03, 1.12)**
Unemployment	1.14 (1.06, 1.23)**	1.02 (0.94, 1.11)
Criminality	1.21 (1.11, 1.32)**	1.10 (0.98, 1.23)
Injuries	1.12 (1.05,1.20)**	1.07 (1.00, 1.15)*
Suicide attempts	1.13 (1.00, 1.29)	1.05 (0.91, 1.22)
Substance use disorders	1.15 (1.04, 1.26)**	1.14 (1.02, 1.26)*
16-17 years		
No graduate degree	1.49 (1.35, 1.65)**	1.13 (1.08, 1.18)**
Unemployment	1.15 (1.06, 1.25)**	1.04 (0.96, 1.11)**
Criminality	1.28 (1.15, 1.42)**	1.17 (1.06, 1.29)**
Injuries	1.12 (1.03, 1.22)**	1.04 (0.97, 1.12)
Suicide attempts	1.17 (1.00, 1.36)*	1.14 (1.02, 1.28)*
Substance use disorders	1.19 (1.06, 1.34)**	1.17 (1.07, 1.29)**

** p value ≤.01, * p value ≤.05

Table S2.A Predictive value of parent- and self-rated attention-deficit/hyperactivity disorder symptoms in females across adolescence on academic, occupational and adverse health outcomes (N=1,507, only females)

	Parent-ratings OR (95% CI)		Self-ratings OR (95% CI)	
	Crude	Adjusted for self-ratings	Crude	Adjusted for parent-ratings
13-14 years				
No graduate degree	1.20(1.07,1.35)**	1.16(1.03,1.30)*	1.08(1.02,1.13)**	1.05(0.99, 1.11)
Unemployment	1.19(1.07,1.33)**	1.18(1.05,1.33)**	1.08(0.99,1.18)	1.05(0.95,1.15)
Criminality	1.29(1.13,1.48)**	1.30(1.09,1.55)**	1.11(0.91,1.36)	0.98(0.75,1.29)
Injuries	1.11(1.00,1.23)	1.10(0.98,1.25)	1.02(0.93,1.12)	1.02(0.92,1.14)
Suicide attempts	1.15(0.99,1.35)	1.15(0.96,1.39)	1.11(0.93,1.31)	1.01(0.83,1.23)
Substance use disorders	1.20(1.05,1.36)**	1.16(1.01,1.33)*	1.15(0.99,1.33)	1.06(0.91,1.24)
16-17 years				
No graduate degree	1.47(1.29,1.67)**	1.39(1.22,1.59)**	1.17(1.11,1.24)**	1.08(1.01,1.15)*
Unemployment	1.24(1.11,1.38)**	1.18(1.05,1.34)**	1.10(1.01,1.20)*	1.07(0.97,1.18)
Criminality	1.42(1.21,1.67)**	1.30(1.02,1.67)*	1.25(1.08,1.45)**	1.25(0.99,1.58)
Injuries	1.12(0.99,1.27)	1.14(1.00,1.29)*	1.03(0.94,1.13)	0.98(0.88,1.09)
Suicide attempts	1.16(0.96,1.40)	1.13(0.90,1.43)	1.08(0.96,1.22)	1.06(0.90,1.25)
Substance use disorders	1.13(0.91,1.40)	1.08(0.83,1.40)	1.10(0.98,1.24)	1.10(0.92,1.32)

** p value ≤.01, * p value ≤.05

Table S3.A Predictive value of parent- and self-rated attention-deficit/hyperactivity disorder symptoms in males across adolescence on academic, occupational and adverse health outcomes (N=1,436, only males)

	Parent-ratings OR (95% CI)		Self-ratings OR (95% CI)	
	Crude	Adjusted for self-ratings	Crude	Adjusted for parent-ratings
13-14 years				
No graduate degree	1.20(1.08, 1.33)**	1.18(1.06, 1.31)**	1.07(1.01, 1.14)*	1.03(0.96, 1.10)
Unemployment	1.08(0.98, 1.20)	1.17(1.06, 1.29)**	0.90(0.79, 1.03)	0.86(0.75, 0.99)*
Criminality	1.15(1.03, 1.29)*	1.12(0.99, 1.26)	1.12(1.01, 1.26)*	1.06(0.93, 1.20)
Injuries	1.14(1.04, 1.24)**	1.11(1.01, 1.23)*	1.11(1.01, 1.22)*	1.05(0.94, 1.17)
Suicide attempts	1.16(0.96, 1.40)	1.21(0.98, 1.51)	1.04(0.81, 1.33)	0.90(0.65, 1.23)
Substance use disorders	1.11(0.97, 1.28)	1.05(0.87, 1.25)	1.20(1.05, 1.37)**	1.14(0.95, 1.36)
16-17 years				
No graduate degree	1.50(1.32, 1.71)**	1.48(1.28, 1.70)**	1.17(1.09, 1.25)**	1.09(1.01, 1.17)*
Unemployment	1.07(0.96, 1.20)	1.16(1.00, 1.34)*	0.90(0.81, 1.01)	0.86(0.75, 0.99)*
Criminality	1.24(1.10, 1.41)**	1.17(0.98, 1.39)	1.17(1.06, 1.29)**	1.08(0.93, 1.26)
Injuries	1.13(1.02, 1.26)*	1.09(0.97, 1.24)	1.10(1.01, 1.21)*	1.04(0.93, 1.15)
Suicide attempts	1.33(1.11, 1.60)**	1.23(0.99, 1.53)	1.14(0.82, 1.56)	1.07(0.81, 1.41)
Substance use disorders	1.25(1.10, 1.43)**	1.14(0.95, 1.37)	1.20(1.06, 1.36)**	1.17(1.00, 1.36)

** p value ≤.01, * p value ≤.05

Table S4.A Predictive value of parent-rated attention-deficit/hyperactivity disorder symptoms, excluding items not present in the self-rating scale, across adolescence on academic, occupational and adverse health outcomes

	Parent-ratings OR (95% CI)	
	Crude	Adjusted for self-ratings
13-14 years		
No graduate degree	1.19 (1.10, 1.28)**	1.18 (1.09, 1.28)**
Unemployment	1.13 (1.05, 1.22)**	1.00 (0.92, 1.08)
Criminality	1.18 (1.08, 1.29)**	1.18 (1.06, 1.31)**
Injuries	1.13 (1.06, 1.21)**	1.10 (1.02, 1.20)*
Suicide attempts	1.15 (1.02, 1.30)*	1.13 (0.96, 1.32)
Substance use disorders	1.16 (1.06, 1.27)**	1.08 (0.96, 1.21)
16-17 years		
No graduate degree	1.40 (1.28, 1.52)**	1.38 (1.26, 1.52)**
Unemployment	1.16 (1.07, 1.25)**	1.03 (0.96, 1.10)
Criminality	1.27 (1.15, 1.42)**	1.21 (1.04, 1.41)*
Injuries	1.13 (1.04, 1.23)**	1.11 (1.01, 1.21)*
Suicide attempts	1.18 (1.01, 1.36)*	1.11 (0.92, 1.33)
Substance use disorders	1.16 (1.03, 1.32)*	1.12 (0.97, 1.30)

** p value ≤.01, * p value ≤.05

Table S5.A Odds of experiencing each adverse socioeconomic and health outcome if individuals score >95% centile compared to <95th centile on ADHD symptoms rated by each informant in early and late adolescence

	Parent-ratings OR (95% CI)	Self-ratings OR (95% CI)
13-14 years		
No graduate degree	2.60 (1.44, 5.10)	1.23 (0.77, 2.02)
Unemployment	2.00 (0.90, 4.00)	1.73 (0.75, 3.55)
Criminality	5.15 (2.12, 10.93)	2.78 (1.03, 6.36)
Injuries	2.03 (0.95, 3.95)	2.41 (1.23, 4.41)
Suicide attempts	2.28 (0.43, 7.72)	1.47 (0.17, 6.03)
Substance use disorders	3.29 (1.30, 7.29)	1.01 (0.20, 3.20)
16-17 years		
No graduate degree	13.32 (4.40, 65.85)	1.83 (1.11, 3.14)
Unemployment	1.79 (0.77, 3.69)	1.23 (0.47, 2.70)
Criminality	3.37 (1.24, 7.87)	1.77 (0.54, 4.51)
Injuries	1.64 (0.71, 3.37)	1.61 (0.73, 3.18)
Suicide attempts	1.68 (0.19, 7.01)	1.45 (0.16, 5.96)
Substance use disorders	3.67 (1.34, 8.36)	1.92 (0.59, 4.94)

Appendix B – Supplementary material for Chapter 4

Supplemental methods

Significance thresholds

For our primary PRS analyses, we selected a conservative significance threshold to control for multiple testing by applying a Bonferroni correction. Euesden et al. (1) recommend using a significance threshold of at least P=0.004 in order to control for the high-resolution scoring approach of selecting the most predictive PRS. As we tested the most predictive PRS across each of the 19 target and control phenotypes, we divided the P-value by the number of tests performed (P=0.004/19), which resulted in a significance threshold of $P=2.1x10^{-4}$.

For our secondary analyses, where we tested the main effects of sex and PRS*sex interaction effects, we selected a conservative significance threshold of P=0.01 as we did not have strong a priori hypotheses of the effects. We applied Bonferroni correction in order to control for the 22 secondary analyses we ran (P=0.01/22), which resulted in a significance threshold of $P=4.5x10^{-4}$.

1: Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. *Bioinformatics*. 2015;31(9): 1466-1468.

Table S1.B List of items in the Verbal-Numerical Reasoning test

Question	Possible answers
Add the following numbers together: 1 2 3 4 5 – is the answer?	13/14/15/16/17/Do not know/Prefer not to answer
Which number is the largest?	642/308/987/714/253/Do not know/Prefer not to answer
Bud is to flower as child is to?	Grow/Develop/Improve/Adult/Old/Do not know/Prefer not to answer
11 12 13 14 15 16 17 18 Divide the sixth number to the right of twelve by three. Is the answer?	5/6/7/8/Do not know/Prefer not to answer
If Truda's mother's brother is Tim's sister's father, what relation is Truda to Tim?	Aunt/Sister/Niece/Cousin/No relation/Do not know/Prefer not to answer
If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from eighty-five. Is the answer?	68/69/70/71/72/Do not know/Prefer not to answer
Stop means the same as?	Pause/Close/Cease/Break/Rest/Do not know/Prefer not to answer
If David is twenty-one and Owen is nineteen and Daniel is nine years younger than David, what is half their combined age?	25/26/27/28/29/Do not know/Prefer not to answer
Age is to years as height is to?	Long/Deep/Top/Metres/Tall/Do not know/Prefer not to answer
150...137...125...114...104... What comes next?	96/95/94/93/92/Do not know/Prefer not to answer
Relaxed means the opposite of?	Calm/Anxious/Cool/Worried/Tense/Do not know/Prefer not to answer
100...99...95...86...70...What comes next?	50/49/48/47/46/45/Do not know/Prefer not to answer
If some flinks are plinks and some plinks are stinks then some flinks are definitely stinks?	False/True/Neither true nor false/Not sure/Do not know/Prefer not to answer

Table S2.B List of items in the Eysenck Personality Inventory Neuroticism scale – Revised (EPIN-R)

Question	**Possible answers**
Does your mood often go up and down?	Yes/No/Do not know/Prefer not to answer
Do you ever feel 'just miserable' for no reason?	
Are you an irritable person?	
Are your feelings easily hurt?	
Do you often feel 'fed-up'?	
Would you call yourself a nervous person?	
Are you a worrier?	
Would you call yourself tense or 'highly strung'?	
Do you worry too long after an embarrassing experience?	
Do you suffer from 'nerves'?	
Do you often feel lonely?	
Are you often troubled by feelings of guilt?	

Note: If individuals responded 'Do not know' or 'Prefer not to answer', they were excluded from analyses.

Table S3.B List of ICD-10 codes for psychiatric diagnoses used as target phenotypes

Psychiatric diagnoses	**ICD-10 codes**
Anxiety and stress-related disorders	
Phobic anxiety disorders	F40
Other anxiety disorders	F41
Obsessive-compulsive disorder	F42
Reaction to severe stress, and adjustment disorders (includes post-traumatic stress disorder)	F43
Depressive disorders	
Depressive episode	F32
Recurrent depressive disorder	F33
Bipolar affective disorder	F31
Schizophrenia, schizotypal and delusional disorders	
Schizophrenia	F20
Schizotypal disorder	F21
Persistent delusional disorders	F22
Acute and transient psychotic disorders	F23
Induced delusional disorder	F24
Schizoaffective disorders	F25
Other nonorganic psychotic disorders	F28
Unspecified nonorganic psychosis	F29
Mental and behavioural disorders due to use of alcohol	
Acute intoxication	F10.0
Harmful use	F10.1
Dependence syndrome	F10.2
Withdrawal state	F10.3
Withdrawal state with delirium	F10.4
Psychotic disorder	F10.5
Amnesic syndrome	F10.6
Residual and late-onset psychotic disorder	F10.7
Other mental and behavioural disorders	F10.8
Unspecified mental and behavioural disorder	F10.9

Table S4.B List of responses for alcohol intake frequency measure

Question	**Possible answers**
About how often do you drink alcohol?	1=Daily or almost daily 2=Three or four times a week 3=Once or twice a week 4=One to three times a month 5=Special occasions only

Note: Answers were reverse-coded and individuals who responded 'Do not know' or 'Prefer not to answer', were excluded from analyses.

Table S5.B Detailed summary of control phenotypes

Phenotype	Description	Covering N genotyped participants	Mean (SD)/ N Cases (%)
Height (cm)	Standing height measured in centimeters during initial assessment	135,495	168.70 (9.21)
Age (years)	Age when attended initial assessment, derived from date of birth and date of attending assessment centre and truncated to whole year	135,726	56.79 (7.96)
Year of initial assessment	Year when participants came in for initial assessment	135,726	2008.57 (0.88)
Number of self-reported cancers	Number of self-reported cancers recorded using a touch-screen self-completed questionnaire followed by an interview at initial assessment	135,146	0.09 (0.31)
Hand grip strength	Hand grip strength of left hand measured using a Jamar J00105 hydraulic hand dynamometer. This measures grip force isometrically in kilograms.	135,163	29.89 (11.35)
Visual acuity	Visual acuity of left eye measured as smallest size letters that are reliably identified at a specified distance. The UK Biobank system is based on a traditional LogMar chart with data captured by Direct Entry to Vox.	29,326	0.02 (0.21)
Menstruating during initial assessment	Question: “Are you menstruating today?” Possible answers: Yes/No/Do not know/Prefer not to answer.	18,829	2,781 (15%)
Sex of baby	Sex of baby refers to the sex of the participants’ child as recorded across all episodes in hospitals. Possible codes: 0=Not known/1=Male/2=Female/3= Indeterminate/9= Not specified.	3,645	2,818 female (77%)

Table S6.B Detailed summary of educational achievement

Description of education variable	**Items**
Education was based on self-report of highest qualification achieved.	1=College or University degree 2=A levels/AS levels or equivalent 3=O levels/GCSEs or equivalent 4=CSEs or equivalent 5=NVQ or HND or HNC or equivalent 6=Other professional qualifications e.g.: nursing, teaching -7=None of the above -3=Prefer not to answer

Note: Participants that replied 'None of the above' or 'Prefer not to answer' were excluded from analyses.

Table S7.B Predictive accuracy of PRS on the target phenotypes after controlling for BMI and educational achievement

	P	**P_T**	**R^2 (%)**
BMI	2.7*10-99	0.121	0.342
Verbal-numerical reasoning	2.9*10-9	0.418	0.070
Alcohol intake frequency	2.7*10-5	0.231	0.013
Risk taking	1.2*10-25	0.291	0.120
Neuroticism	3.5*10-12	0.139	0.045
Tobacco use	1.6*10-13	0.488	0.230
Depressive disorder	1.7*10-8	0.033	0.067
Alcohol dependency	2.6*10-5	0.175	0.177
Anxiety disorder	0.005	0.116	0.037
Bipolar disorder	0.041	0.117	0.022
Schizophrenia	0.280	0.263	0.032

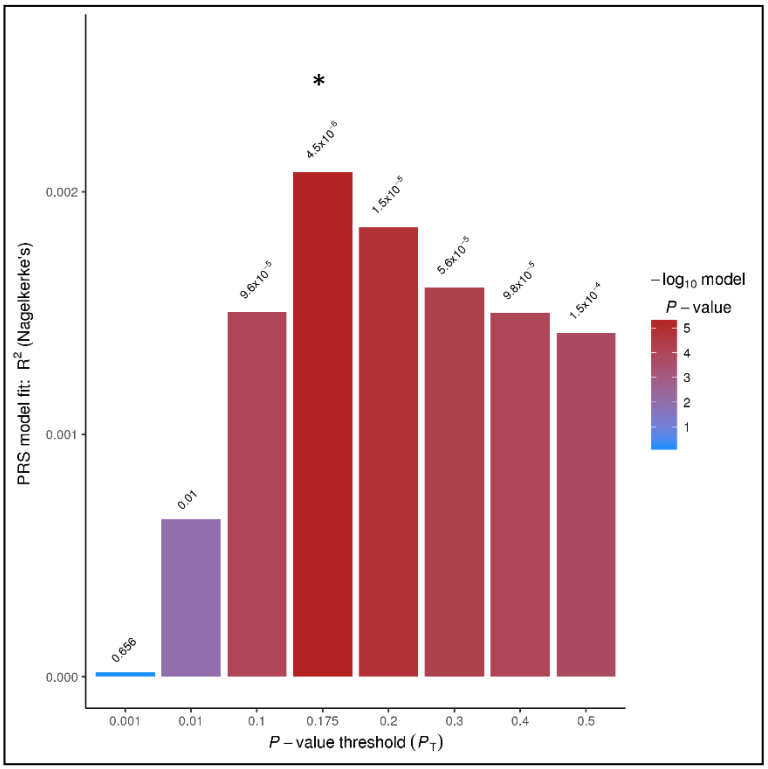

Figure S1.B Plot for alcohol dependency

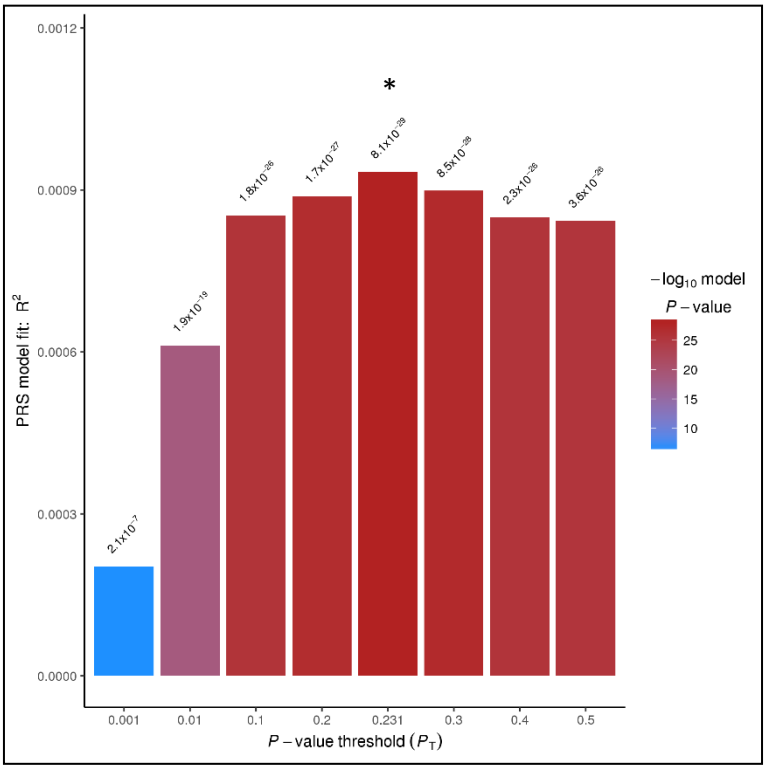

Figure S2.B Plot for alcohol intake frequency

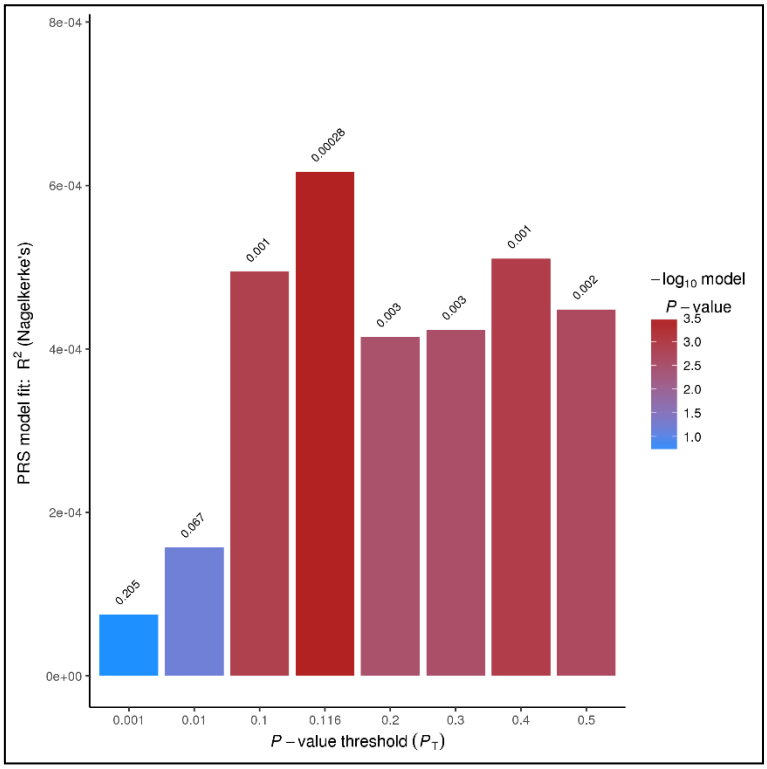

Figure S3.B Plot for anxiety

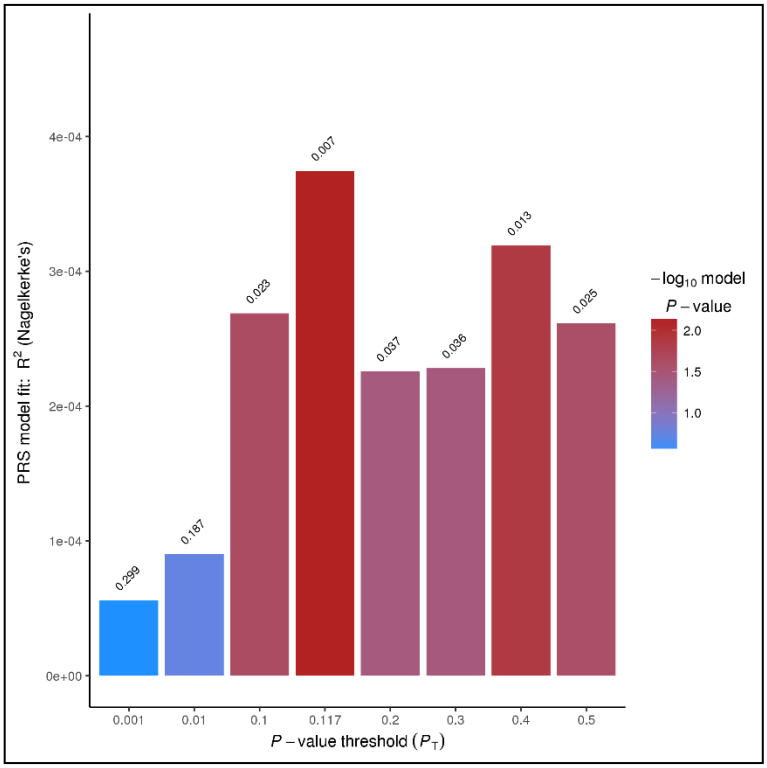

Figure S4.B Plot for bipolar disorder

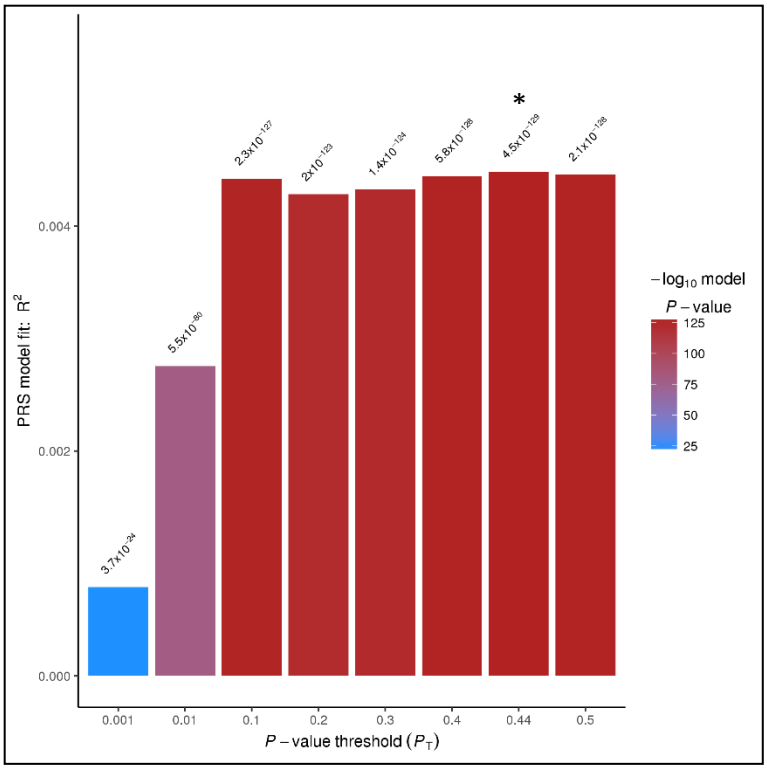

Figure S5.B Plot for BMI

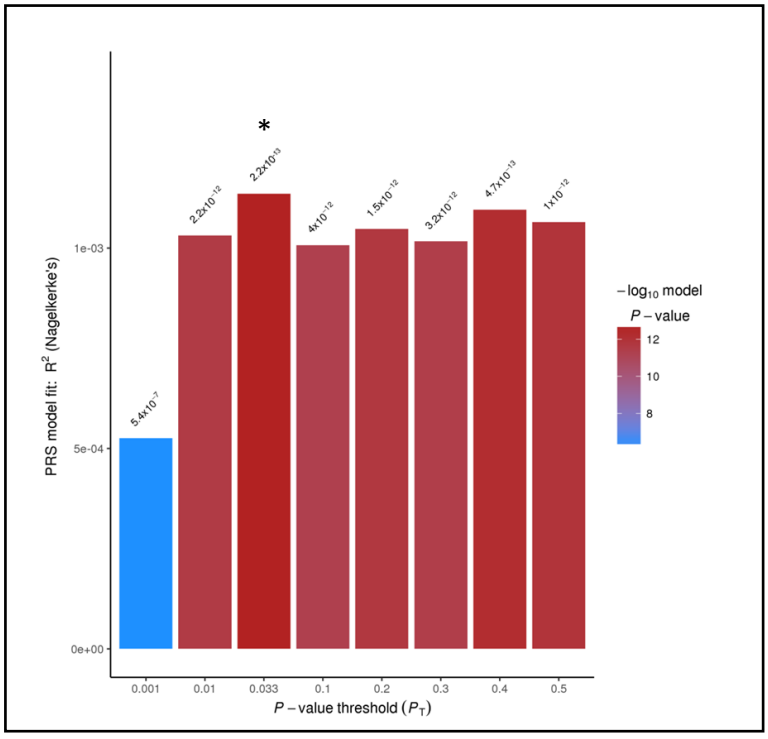

Figure S6.B Plot for depressive disorder

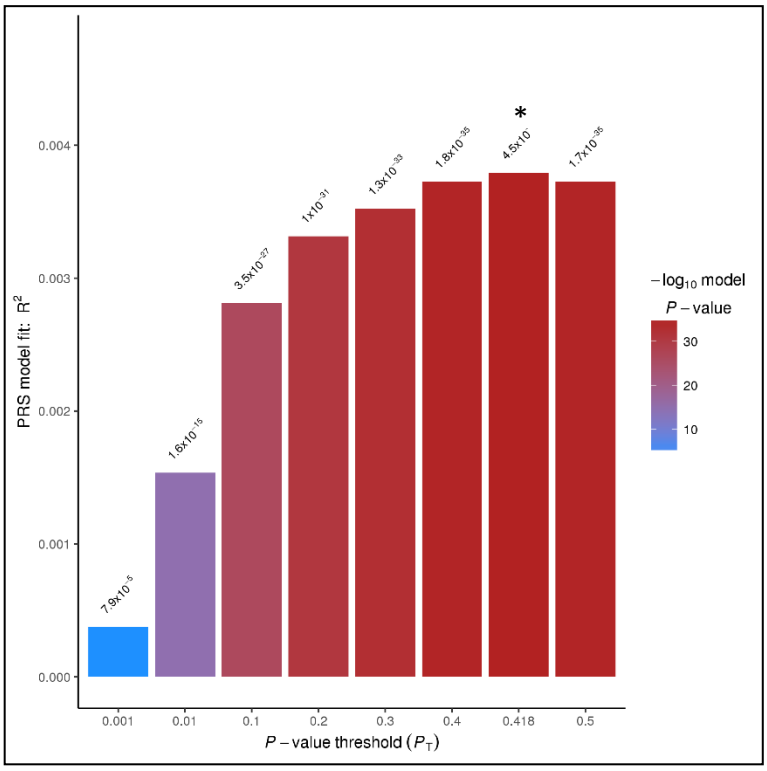

Figure S7.B Plot for verbal-numerical reasoning

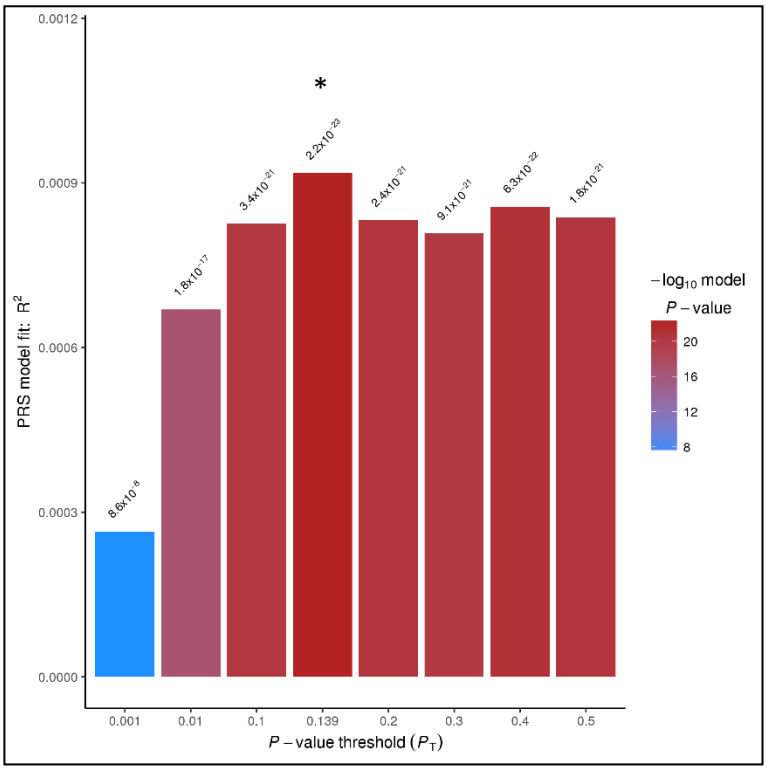

Figure S8.B Plot for neuroticism

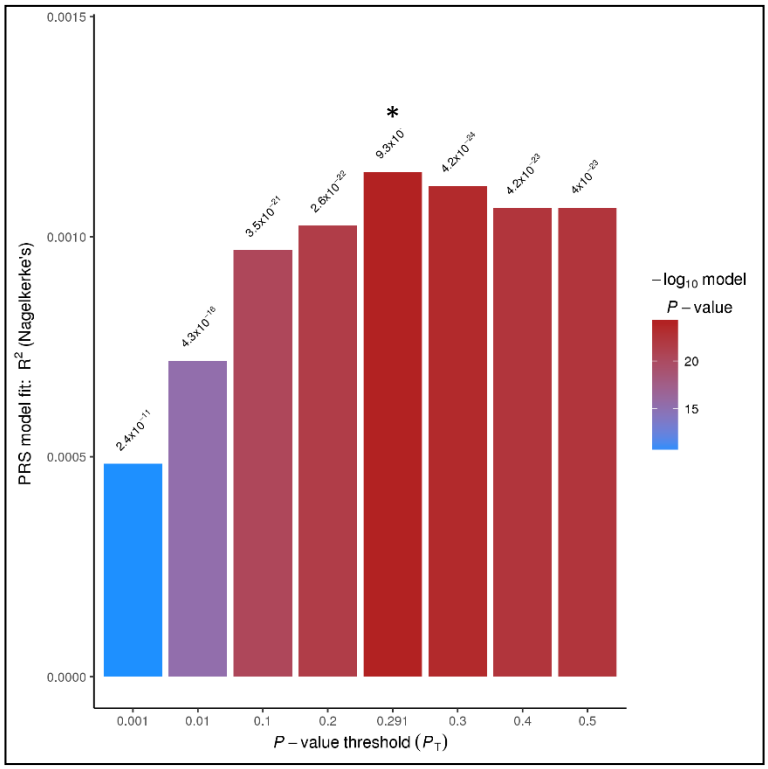

Figure S9.B Plot for risk taking

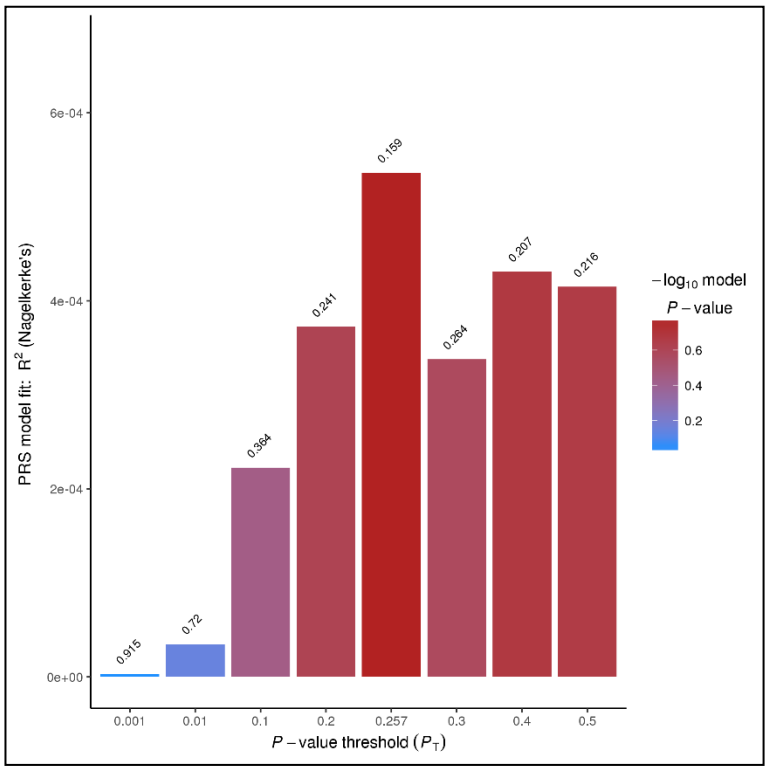

Figure S10.B Plot for schizophrenia

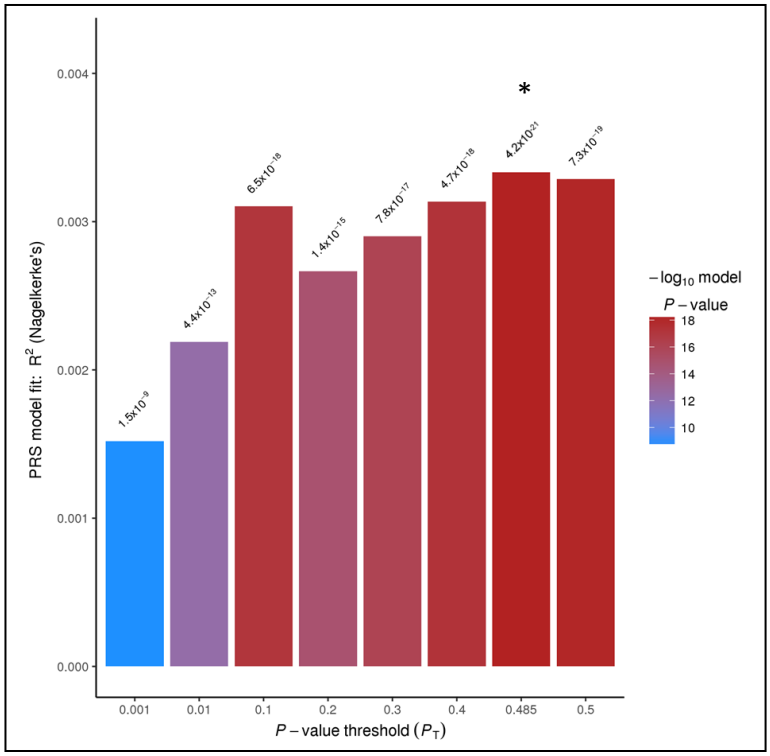

Figure S11.B Plot for tobacco use

Note: P-value threshold represents the P-value at the cut-off for inclusion of single-nucleotide polymorphisms in the polygenic risk score. Values on top of the bars represent P-values for the regression models.

* p-value below significance threshold for the most predictive PRS.

Appendix C – Supplementary material for Chapter 5

Table S1.C Associations between skin conductance measures and oppositional defiant disorder/conduct disorder symptoms within each (ADHD and control) group

	NSFs				**SCL**			
	ADHD		Controls		ADHD		Controls	
ODD/CD	*Beta*	*p*	*Beta*	*p*	*Beta*	*p*	*Beta*	*p*
Rest1	0.01	0.92	0.04	0.50	-0.15	0.41	0.03	0.63
CPT	-0.04	0.79	0.02	0.77	-0.15	0.33	0.05	0.48
Fast Task	0.05	0.40	-0.02	0.78	0.11	0.44	-0.01	0.98
Rest 2	-0.04	0.77	0.09	0.13	-0.03	0.85	-0.02	0.84

ODD/CD: Oppositional defiant disorder/conduct disorder symptoms. CPT: Continuous performance task. SCL: Skin conductance level. NSFs: non-specific fluctuations per second.

* p-value < 0.05 after controlling for ADHD symptoms

Table S2.C Pair-wise tests between groups (ADHD and control) in each condition on skin conductance measures: Controlling for IQ

Condition		**ADHD case-control comparison**		
		t	**p**	**Cohen's d**
Rest time 1	*SCL*	-0.44	0.66	-.07
	NSF	0.50	0.62	.08
CPT	*SCL*	0.20	0.84	.03
	NSF	0.40	0.69	.06
Fast Task	*SCL*	-1.17	0.24	-.09
	NSF	2.48	**0.01**	.38
Rest time 2	*SCL*	0.68	0.50	.10
	NSF	2.37	**0.02**	.36

CPT: Continuous performance task. SCL: Skin conductance level. NSF: non-specific fluctuations per second.

Table S3.C Main and interaction associations between skin conductance and IQ

	NSFs				**SCL**			
	Main		Interaction		Main		Interaction	
IQ	*Beta*	*p*	*Beta*	*p*	*Beta*	*p*	*Beta*	*p*
Rest1	0.02	0.80	0.18	0.20	**0.14**	**0.04**	0.22	0.21
CPT	0.05	0.48	0.17	0.27	**0.17**	**0.02**	0.30	0.09
Fast Task	0.02	0.77	-0.07	0.62	**0.40**	**<0.01**	0.10	0.49
Rest 2	-0.01	0.96	0.02	0.89	**0.17**	**0.02**	0.04	0.83

CPT: Continuous performance task. SCL: Skin conductance level. NSF: non-specific fluctuations per second.

Table S4.C Pair-wise tests between groups (ADHD and control) in each condition on skin conductance measures: Controlling for age and gender

Condition		**ADHD case-control comparison**			
		t	**df**	**p**	**Cohen's d**
Rest time 1	*SCL*	-1.31	176	0.19	-0.20
	NSF	0.27	175	0.78	0.04
CPT	*SCL*	-0.90	188	0.37	-0.13
	NSF	-0.11	188	0.91	0.02
Fast Task	*SCL*	-3.71	171	**<.01**	-0.57
	NSF	1.98	173	**0.05**	0.30
Rest time 2	*SCL*	-0.39	180	0.70	-0.06
	NSF	2.04	177	**0.04**	0.31

CPT: Continuous performance task. SCL: Skin conductance level. NSF: non-specific fluctuations per second.

Appendix D – Supplementary material for Chapter 6

Table S1.D Means and standard deviations of EEG frequency bands within each region during each Time points (Pre- and Post-intervention) and Session (Exercise and Resting control) during the CPT-OX

	Exercise intervention		**Resting control**	
	Pre	**Post**	**Pre**	**Post**
Delta				
frontal	5.21 (4.63)	7.20 (7.63)	5.35 (3.66)	5.18 (2.21)
central	2.42 (2.25)	3.31 (2.19)	2.37 (1.16)	3.11 (3.24)
parietal	3.94 (2.63)	5.81 (4.23)	4.18 (2.38)	4.66 (2.46)
Theta				
frontal	0.65 (0.63)	0.81 (0.74)	0.73 (0.75)	0.85 (0.80)
central	0.32 (0.23)	0.42 (0.35)	0.39 (0.32)	0.48 (0.39)
parietal	0.62 (0.70)	0.79 (0.92)	0.76 (0.96)	0.86 (0.96)
Alpha				
frontal	0.79 (1.72)	0.94 (1.64)	0.84 (1.70)	0.98 (1.75)
central	0.48 (0.74)	0.58 (0.70)	0.55 (0.88)	0.68 (0.97)
parietal	1.21 (2.45)	1.66 (2.87)	1.42 (2.88)	1.67 (2.83)
Beta				
frontal	0.14 (0.09)	0.19 (0.18)	0.15 (0.11)	0.16 (0.07)
central	0.08 (0.04)	0.09 (0.05)	0.09 (0.06)	0.10 (0.05)
parietal	0.12 (0.05)	0.16 (0.08)	0.14 (0.07)	0.15 (0.07)

EEG: Electroencophalogram, CPT-OX: Cued Continuous Performance Task

Table S2.D All main and interaction effects of Time (Pre- and Post-intervention), Condition (Exercise and Resting control) and Region (Frontal, Central and Parietal) on cognitive and brain measures during the Continuous Performance Task

		Chi^2	**P-value**
MRT	Condition	1.96	0.16
	Time	0.03	0.87
	ConditionxTime	0.36	0.55
RTV	Condition	0.14	0.71
	Time	5.19	0.02
	ConditionxTime	0.73	0.39
OE	Condition	3.24	0.07
	Time	4.12	0.04
	ConditionxTime	0.02	0.89
CE	Condition	1.08	0.30
	Time	11.30	0.001
	ConditionxTime	0.14	0.71
CNV	Condition	0.77	0.38
	Time	1.63	0.20
	ConditionxTime	0.21	0.65
Cue P3	Condition	0.41	0.52
	Time	0.15	0.70
	ConditionxTime	0.01	0.94
NoGo P3	Condition	0.25	0.61
	Time	4.75	0.03
	ConditionxTime	0.03	0.87
Go P3	Condition	0.21	0.65
	Time	2.28	0.13
	ConditionxTime	4.97	0.03
Delta	Condition	3.12	0.08

	Time	11.09	<.001
	Region	66.18	<.001
	ConditionxTime	5.20	0.02
	ConditionxRegion	1.52	0.47
	TimexRegion	0.43	0.80
	ConditionxTimexRegion	1.98	0.37
Theta	Condition	0.4.16	0.04
	Time	11.83	0.001
	Region	83.04	<.001
	ConditionxTime	0.44	0.51
	ConditionxRegion	0.28	0.87
	TimexRegion	0.33	0.85
	ConditionxTimexRegion	0.11	0.95
Alpha	Condition	0.57	0.45
	Time	3.59	0.06
	Region	52.15	<.001
	ConditionxTime	0.07	0.80
	ConditionxRegion	0.07	0.96
	TimexRegion	0.99	0.61
	ConditionxTimexRegion	0.22	0.89
Beta	Condition	0.01	0.98
	Time	9.16	0.003
	Region	60.26	<.001
	ConditionxTime	1.17	0.28
	ConditionxRegion	1.98	0.37
	TimexRegion	0.92	0.63
	ConditionxTimexRegion	1.59	0.45

MRT: Mean reaction time, RTV: Reaction time variability, OE: Omission error, CE: Commission error, CNV: Contingent negative variation.

Table S3.D Means and standard deviations of cognitive and brain measures during each Time point (Pre- and Post-intervention) and Condition (Exercise and Resting control) during the Eriksen Flanker Task

	Exercise intervention		**Resting control**	
	Pre	**Post**	**Pre**	**Post**
Errors (Cong)	2.84 (2.48)	3.88 (3.64)	2.92 (2.45)	4.04 (3.40)
Errors (Incong)	44.88 (15.66)	41.92 (15.17)	42.35 (14.58)	41.35 (14.27)
MRT (Cong)	321.67 (35.85)	318.08 (35.11)	328.37 (39.43)	322.41 (36.21)
MRT (Incong)	402.38 (41.33)	394.97 (41.15)	410.22 (45.69)	402.36 (36.92)
RTV (Cong)	69.27 (25.11)	76.20 (32.14)	74.84 (29.29)	76.89 (33.20)
RTV (Incong)	62.60 (24.52)	69.51 (25.62)	68.37 (25.10)	70.43 (25.31)
N2 (Cong)	-2.49 (1.93)	-1.80 (2.16)	-2.12 (2.21)	-1.77 (1.20)
N2 (Incong)	-1.83 (1.87)	-1.39 (1.95)	-1.97 (2.31)	-1.68 (2.06)
ERN	-6.22 (3.56)	-5.33 (3.24)	-6.31 (3.27)	-5.83 (2.69)
Pe	7.03 (3.52)	8.09 (4.61)	6.45 (4.61)	7.32 (5.03)
Delta	5.15 (8.12)	4.57 (3.35)	5.94 (11.20)	5.28 (10.94)
Theta	0.67 (0.65)	0.73 (0.68)	0.75 (0.85)	0.76 (0.70)
Alpha	0.89 (1.55)	1.03 (1.61)	0.95 (1.81)	0.98 (1.60)
Beta	0.15 (0.18)	0.15 (0.14)	0.13 (0.12)	0.15 (0.10)

Cong: Congruent trial, Incong: Incongruent trial, MRT: Mean reaction time, RTV: Reaction time variability. Average EEG frequency band measures are reported across all brain regions.

Table S4.D Means and standard deviations of cognitive and brain measures during each Time point (Pre- and Post-intervention) and Condition (Exercise and Resting control) during the Fast Task

	Exercise intervention		**Resting control**	
	Pre	**Post**	**Pre**	**Post**
MRT	49.84 (10.37)	52.33 (17.16)	54.70 (22.50)	55.78 (22.64)
RTV	13.62 (16.20)	21.70 (31.60)	24.57 (39.92)	24.20 (37.99)
P3	6.30 (3.69)	4.90 (5.56)	6.56 (3.90)	5.69 (4.79)
Delta	3.57 (2.56)	4.12 (3.49)	3.42 (2.71)	4.01 (3.21)
Theta	0.64 (0.73)	0.66 (0.69)	0.66 (0.77)	0.74 (0.86)
Alpha	0.90 (1.66)	0.89 (1.33)	0.97 (1.71)	0.98 (1.64)
Beta	0.13 (0.08)	0.13 (0.09)	0.14 (0.09)	0.15 (0.10)

MRT: Mean reaction time, RTV: Reaction time variability. Average EEG frequency band measures are reported across all brain regions.

Table S5.D Main and interaction effects of Time (Pre- and Post-intervention), Condition (Exercise and Resting control) and Region (Frontal, Central and Parietal) on cognitive and brain measures in **Eriksen Flanker Task**

	Chi2	**P-value**
Errors (Congruent)		
Time	4.87	0.03
Errors (Incongruent)		
NS		
MRT (Congruent)		
Session	5.93	0.01
MRT (Incongruent)		
Session	7.16	0.01
Time	6.45	0.01
RTV (Congruent)		
NS		
RTV (Incongruent)		
NS		
N2 (Congruent)		
Time	7.91	0.01
N2 (Incongruent)		
Time	4.35	0.04
ERN (Incongruent)		
Time	6.10	0.01
Pe (Incongruent)		
Time	8.71	0.01
Delta		
Region	22.74	<.001
Theta		
Region	88.92	<.001
Alpha		
Region	87.76	<.001
Beta		
Region	99.90	<.001

MRT: Mean reaction time, RTV: Reaction time variability, NS: Not significant. Only significant main and interaction effects are reported.

Table S6.D Main and interaction effects of Time (Pre- and Post-intervention), Condition (Exercise and Resting control) and Region (Frontal, Central and Parietal) on cognitive and brain measures in **Fast Task**

	Chi2	**P-value**
MRT		
Condition	5.69	0.02
RTV		
Condition	3.74	0.05
P3		
NS		
Delta		
Region	103.90	<.001
Time	5.44	0.02
Theta		
Region	99.85	<.001
Alpha		
Region	75.04	<.001
Beta		
Region	98.04	<.001
Condition	4.95	0.03

MRT: Mean reaction time, RTV: Reaction time variability, NS: Not significant. Only significant main and interaction effects are reported.